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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JULY, 1930

ORIGINAL ARTICLES.

THE EFFECT OF SINGLE MASSIVE DOSES OF LIVER EXTRACT ON PATIENTS WITH PERNICIOUS ANEMIA.

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IN 1926 Minot and Murphy demonstrated[1] that, when sufficient amounts of liver were included in the diet of patients with pernicious anemia, prompt and enduring remissions invariably occurred. Later, aided by Cohn[2] and others, they showed that the active substance in liver which produces this effect can be extracted from liver in concentrated form. Now various extracts of liver, which contain in small bulk its therapeutic value, are available for general use. Such liver extracts have obvious practical advantages in the study and treatment of pernicious anemia, since, freed from most of the substances present in liver, the potent material can easily be administered in concentrated form in large amounts. The customary dosage of liver given to patients with pernicious anemia is that originally recommended by Minot and Murphy,[1] that is, 125 to 240 gm. daily. If liver extract is used, somewhat larger daily doses (extract derived from 300 to 600 gm. of fresh liver) are ordinarily required.

Minot, Murphy, Cohn and their associates[2] have also studied the relation of the amounts of liver extract used to the reticulocyte response and find that when the extract derived from 300 gm. of liver is administered daily a satisfactory response is produced. If a greater amount of extract (from 600 gm. of liver) is given daily, the response is similar in magnitude but occurs more rapidly. If lesser amounts of extract are used the rise in the percentage of reticulocytes may occur but is less in magnitude, is more delayed and is more prolonged. They believe that "within certain limits the response tends to depend upon the total amount of extract given rather than the daily dose."

This observation and the experience of Bloomfield[3] who produced a complete remission in a patient with sprue with a single large dose of liver extract suggested the study of the effects of single, massive doses of liver extract in pernicious anemia which is reported in this paper.

Material and Methods. The effects of single, massive doses of liver extract were studied intensively in 4 patients with typical pernicious anemia over periods of from twenty-two to thirty-seven days. In 3 patients a single dose of thirty vials of Lilly's liver extract No. 343 (equivalent to 3000 gm. of liver) was given. To the fourth patient half this amount or fifteen vials of liver extract was used as a single dose. No further medication was given to any of these patients until the resultant reticulocyte response was completed.

The required amount of liver extract, dissolved in 200 or 300 cc. of water, was usually given by stomach tube since in such large amounts liver extract taken by mouth is extremely nauseating and cannot be retained when swallowed. Even when introduced by stomach tube considerable amounts of liver extract, mixed with gastric juice and saliva, were vomited within a half hour. When this occurred the vomited material was filtered and returned by stomach tube, and was retained. Following the administration of the liver extract in this fashion, the patients complained of nausea and a sensation of fullness in the epigastrium which disappeared within an hour as the patient lay quietly in bed. As these symptoms disappeared there was increased intestinal activity, followed by a profuse watery diarrhea in about an hour. After the passage of several liquid stools no further discomfort was experienced. Except for the transitory nausea and diarrhea, no ill effects from these very large doses of liver extract were observed.

Observations on the changes occurring in the blood were made at frequent intervals. In 3 patients the percentage of reticulocytes was estimated at four-hour intervals day and night during the reticulocyte response; in the fourth patient at twelve-hour intervals. The numbers of red blood cells and white blood cells were counted and the amount of hemoglobin in the blood was determined at

least every twelve hours and in one patient every four hours. The changes in the microscopic character of the various types of blood cells were also carefully studied at intervals of four to twelve hours.

All estimations were performed with standardized instruments and with the usual precautions to insure accuracy.

Case Reports. Each patient gave a characteristic history of pernicious anemia and the physical and laboratory findings were typical of this disease. In every patient the characteristic response and improvement of blood followed liver medication.

Case A.—Mr. H. R., aged sixty-three years, entered the hospital during a second relapse on May 14, 1928. The initial blood findings were: Red blood cell count, 2,370,000 per c.mm.; white blood cell count, 2120 per c.mm.; hemoglobin, 57 per cent (Sahli). On May 16 he was given fifteen vials of Lilly's liver extract No. 343 at 8 P.M. by stomach tube. No further medication was given until May 29, when daily doses of thirty capsules of Abbott's liver extract were begun. At the time of discharge, June 4, 1928, the blood findings were: Red blood cell count, 3,780,000 per c.mm.; white blood cell count, 9850 per c.mm.; hemoglobin, 77 per cent (Sahli).

Case B.—Mr. A. B., aged fifty-four years, was studied during his first relapse. On entering the hospital, May 17, 1928, his initial blood findings were: Red blood cell count, 1,870,000 per c.mm.; white blood cell count, 5600 per c.mm.; hemoglobin, 50 per cent (Sahli). On May 18, at 4 P.M., thirty vials of Lilly's liver extract No. 343 were administered by stomach tube. No further medication was given until May 30, when four vials of Lilly's liver extract No. 343 were given daily. When discharged, June 12, 1928, the blood findings were: Red blood cell count, 2,670,000 per c.mm.; white blood cell count, 8300 per c.mm.; hemoglobin, 75 per cent (Sahli).

Case C.—Mr. J. R., aged fifty-five years, was studied during his third relapse. On May 8, 1928, before treatment the blood findings were: Red blood cell count, 1,430,000 per c.mm.; white blood cell count, 3300 per c.mm.; hemoglobin, 32 per cent (Sahli). On May 8, at 8 A.M., thirty vials of Lilly's liver extract No. 343 were given by stomach tube. No further medication was given until May 25, when at 4 P.M., a second dose of thirty vials of Lilly's liver extract No. 343 was administered by stomach tube. On June 2 the daily administration of four vials of Lilly's liver extract No. 343 was begun. When he was discharged on June 20, 1928, the blood findings were: Red blood cell count, 3,910,000 per c.mm.; white blood cell count, 6000 per c.mm.; hemoglobin, 76 per cent (Sahli).

Case D.—Mr. B. P., aged forty-two years, entered the hospital on May 18, 1928, during his second relapse, in a semicomatose condition. The initial blood findings then were: Red blood cell count, 690,000 per c.mm.; white blood cell count, 4900 per c.mm.; hemoglobin, 15 per cent (Sahli). On May 19, at 8 A.M., he was given thirty vials of Lilly's liver extract No. 343 by stomach tube. No further medication was given until June 1, when daily doses of thirty capsules of Abbott's liver extract were begun. When discharged on June 20, 1928, his blood findings were: Red blood cell count, 2,400,000 per c.mm.; white blood cell count, 6250 per c.mm.; hemoglobin, 42 per cent (Sahli).

Clinical Effects of a Single Massive Dose of Liver Extract. The immediate clinical response of patients with pernicious anemia to

the administration of a single, massive dose of liver extract compares favorably with that obtained when adequate smaller daily doses are given. The increase of appetite, strength and sense of well being, and the decrease of pallor and icterus are similar in either case although improvement begins somewhat earlier following the administration of massive single doses. Ordinarily, when three to six vials of liver extract are given daily, evidence of clinical improvement is seen in from three to four days after liver medication has been started. Patients receiving a single dose of thirty vials of liver extract begin to show clinical improvement after two days. One patient (Mr. B. P.), who was semicomatose and, being nauseated, was unable to retain food, regained consciousness and appetite within twenty-four hours after the administration of thirty vials of liver extract.

The Reticulocyte Response to Single Large Doses of Liver Extract. The reticulocyte response to liver treatment in patients with pernicious anemia serves, as Minot[2] has emphasized, as a valuable index of the effectiveness of treatment, and is therefore, from a practical standpoint, a most important feature of early remission. The nature of this response and the important factors influencing it are well known to consist of a rise and a subsequent fall in the numbers and the percentage of erythrocytes containing reticulum during the first two weeks of liver treatment. The important features of the reticulocyte response are its magnitude and the rate at which it takes place.

The magnitude of the response is measured either by the concentration of reticulocytes (million per c.mm. of blood) when their percentage is greatest or by the maximum percentage of reticulocytes observed during the reticulocyte response. Minot and his associates,[2] by studying the data obtained from groups of patients with varying degrees of anemia, have made the observation, which has been confirmed by others, that the magnitude of the reticulocyte response varies inversely with the red blood cell count before treatment. They have found empirically that the relationship between the red blood cell count of the patient before treatment (Eo), and the expected maximum concentration of reticulocytes (Epr) in millions per cmm. of blood can be expressed by the formula: $Epr = 0.73 - 0.2\ Eo$. In our experience this formula is satisfactory, and may be used to determine whether treatment in any given case has been efficient.

The rate at which changes in the percentage of reticulocytes occur is measured by the time intervals between the first administration of liver and the beginning, peak, and end of the increase of reticulocytes. Ordinarily the reticulocytes begin to increase about three days after treatment begins, rise to their greatest numbers on the seventh or eighth day, and return to a normal percentage (approximately 2 per cent) in about two weeks if the daily dosage

of liver is 300 gm. or an equally effective amount of liver extract. If larger amounts of liver material are given, these changes tend to occur earlier. The first rise in percentage may appear as early as the second day, the maximum percentage by the fifth or sixth day, and the end of the increase by the tenth or twelfth day if maximal amounts of liver (600 gm. or more) or liver extract are used daily.

Judged by these standards the reticulocyte responses obtained after the administration of single, massive doses of liver extract, were satisfactory in the 4 patients studied. The significant data are shown in the table. That the response obtained in each case was approximately of the expected magnitude may be seen by a comparison of the concentration of reticulocytes observed at the peak of the reticulocyte rise and the concentration estimated by the formula: $Epr = 0.73 - 0.2\ Eo$.

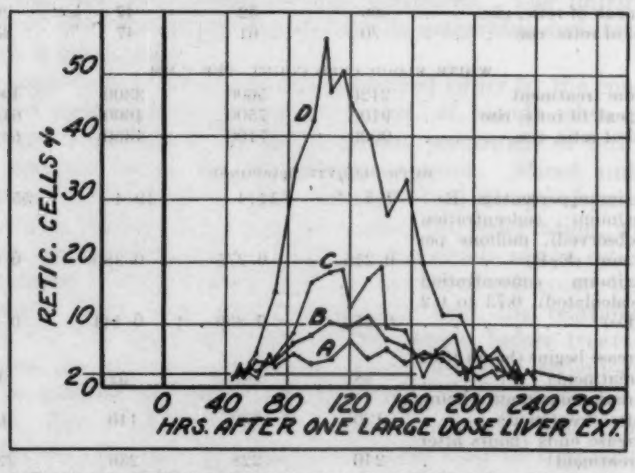
EFFECTS OF SINGLE MASSIVE DOSES OF LIVER EXTRACT.

Patients.	A. Mr. H. R.	B. Mr. A. B.	C. Mr. J. R.	D. Mr. B. P.
RED BLOOD CELL COUNT, MILLIONS PER C.MM.				
Before treatment (Eo)	2.37	1.87	1.43	0.69
At peak of retic. rise (Ep)	2.86	2.41	1.99	1.12
End of retic. response	3.56	2.71	2.11	1.57
HEMOGLOBIN (SAHLI).				
Before treatment	57	50	32	15
At peak of retic. rise	66	52	47	20
End of retic. rise	70	61	47	35
WHITE BLOOD CELL COUNT, PER C.MM.				
Before treatment	2120	5600	3300	4900
At peak of retic. rise	9100	7500	4600	6150
End of retic. rise	9600	7100	4350	5850
RETICULOCYTE RESPONSE.				
Maximum percentage (R)	7.5	11.4	19.4	55.7
Maximum concentration (observed), millions per c.mm. (EpR)	0.215	0.275	0.386	0.624
Maximum concentration (calculated), 0.73 to 0.2 (Eo)	0.256	0.356	0.444	0.592
Increase begins (hours after treatment)	48	48	52	48
Increase maximum (hours after treatment)	120	132	140	104
Increase ends (hours after treatment)	240	228	236	228
Duration retic. increase (hours)	192	180	184	180
DOSAGE OF LIVER EXTRACT.				
Vials of liver extract (one vial 100 gm. liver)	15	30	30	30

The rate of the reticulocyte response was remarkably constant in the 4 patients studied. The first rise in the percentage of the reticu-

locytes above 2 per cent, the upper limit of normal, was seen forty-eight hours after the administration of the liver extract in 3 patients and in fifty-two hours in the fourth. The highest percentage of reticulocytes occurred between one hundred and four and one hundred and forty hours after the administration of the large dose of liver extract. The last elevated reticulocyte figure (that is, the end of the reticulocyte response) was seen between two hundred and twenty-eight and two hundred and forty hours after liver extract was given. The duration of the elevated reticulocyte percentage varied between one hundred and eighty and one hundred and ninety-two hours in the 4 cases. In terms of days, the response of the reticulocytes began at the end of two days, reached a maximum in five or six days, and was ended during the tenth day after the administration of a single large dose of liver extract, the rate of the response being that which is seen under the most favorable circumstances when liver extract is given in large daily doses. The remarkable constancy of the response in these 4 patients is shown graphically in Chart I.

CHART I.—DURATION AND MAGNITUDE OF RETICULOCYTE RESPONSE AFTER A SINGLE LARGE DOSE OF LIVER EXTRACT WITH VARYING DEGREES OF ANEMIA BEFORE TREATMENT.



A, Patient A; *B*, Patient B; *C*, Patient C; *D*, Patient D. (See table.)

The percentages of reticulocytes, when measured every four hours, showed certain variations. Minor fluctuations up or down often were seen, which apparently had no significance and were considered to be chance variations incident to the measurement of the percentage of reticulocytes. As contrasted to these chance variations a fairly regular daily variation of the percentage of

reticulocytes was observed except during a rapid increase or decrease in their numbers. Similar daily variations have been observed by Porter and Irving.[4] Thus, during a twenty-four hour period, the highest percentages of reticulocytes most often occurred at night, usually at midnight or 4 A.M., and the lowest percentages in the daytime, usually between 8 A.M. and 4 P.M. with the patients at rest in bed. During the reticulocyte response the numbers of reticulocytes may increase or decrease greatly within a four-hour period. When rapidly changing in numbers, the reticulocyte percentage sometimes fell or rose as much as 20 per cent within four hours when the reticulocyte response was great, as in patient B. P.

"Blast Crises." The finer microscopic changes in the blood cells of the 3 patients who received thirty vials of liver extract in a single dose, were studied carefully for each four-hour period during the early part of the remission. In all 3 there occurred a so-called "blast crisis" similar to those observed by Minot[2] in patients receiving daily doses of liver. In each patient immature forms of both red and white blood cells appeared in the blood smears shortly after the administration of liver extract.

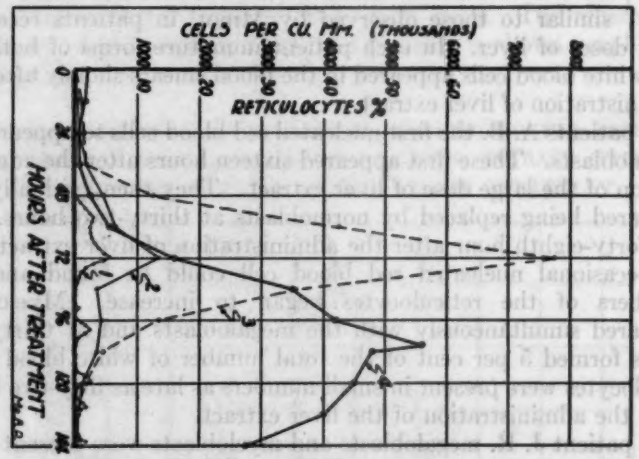
In patients A. B. the first nucleated red blood cells to appear were megaloblasts. These first appeared sixteen hours after the administration of the large dose of liver extract. They then gradually disappeared being replaced by normoblasts at thirty-two hours. By the forty-eighth hour after the administration of liver extract only an occasional nucleated red blood cell could be found and the numbers of the reticulocytes began to increase. Myelocytes appeared simultaneously with the megaloblasts and at thirty-two hours formed 5 per cent of the total number of white blood cells. Myelocytes were present in small numbers as late as fifty-two hours after the administration of the liver extract.

In patient J. R. megaloblasts and myeloblasts were present eight hours after the liver extract was given. They increased in numbers until the thirty-sixth hour when normoblasts and myelocytes were seen. The megaloblasts then decreased in numbers as the normoblasts increased. Nucleated red blood cells and immature white blood cells of myeloid origin persisted for sixty hours after the administration of liver extract although with appearance of increased numbers of reticulocytes beginning at forty-eight hours these cells were found only occasionally. In both patients other evidences of immaturity, such as Howell-Jolly bodies and Cabot ring bodies were occasionally noticed in red blood cells during the period of the "crisis."

A most remarkable "crisis" occurred in patient B. P. whose red blood cell count before treatment was 690,000 per c.mm. Megaloblasts, normoblasts and myelocytes were observed in the blood twelve hours after the administration of liver extract (Chart II). Myeloblasts were present at twenty-four hours. The numbers of

the nucleated red blood cells and immature white blood cells increased to reach their maximum numbers seventy-two hours after the giving of the liver extract, decreasing rapidly in numbers thereafter. They were present in small numbers as late as one hundred and forty-four hours after the administration of liver extract. Hemohistioblasts appeared at forty-eight hours, reached a maximum number at seventy-two hours and were present in small numbers as late as one hundred and fifty-two hours after the giving of liver extract. At seventy-two hours the point at which the "crisis" was at its maximum, myelocytes were present in a concentration of 973 per c.mm. of blood, myeloblasts in a concentration of 343 per c.mm., hemohistioblasts 548 per c.mm. and nucleated red blood cells 7746 per c.mm. Among the nucleated red blood cells the megaloblast was the dominant type of cell during the early part of the "crisis;" the normoblast during the later part. Other peculiar forms of immature red blood cells were seen during this period of intense hematopoietic response, Cabot ring bodies, Howell-Jolly bodies and Isaacs' granules and in a few instances red blood cells exhibiting mitotic figures being observed.

CHART II.—UNUSUAL CRISIS OF IMMATURE MYELOID CELLS AFTER LARGE DOSE OF LIVER EXTRACT.



1. Numbers of hemohistioblasts per cubic millimeter of blood. 2. Numbers of immature myeloid white blood cells (myelocytes and myeloblasts) per cubic millimeter. 3. Numbers of nucleated red blood cells (megaloblasts and normoblasts) per cubic millimeter. 4. Percentage of reticulocytes.

In these 4 patients it is interesting to point out that immature myeloid cells appeared in considerable numbers preceding the increase in numbers of reticulocytes. Blast crises have been observed

to occur spontaneously in patients with pernicious anemia, but as Minot[2] has suggested, the crises following the stimulation of the bone marrow by liver have a different significance than those developing spontaneously. Spontaneous blast crises in pernicious anemia have in some instances been regarded as an unfavorable sign which precedes death and as an evidence of bone marrow failure. The blood crises following liver medication, such as those described above, seem to be evidence of an intense stimulation of the bone marrow to hematopoietic activity and have a favorable rather than an unfavorable significance.

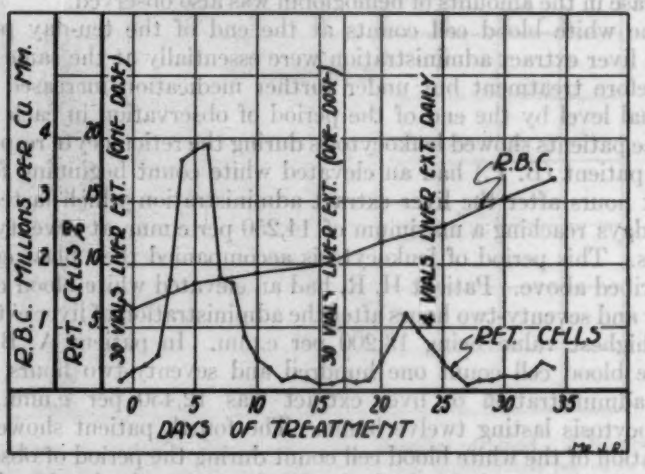
Increase of Numbers of Red and White Blood Cells and of Amount of Hemoglobin. As may be seen in the table there was a satisfactory increase in the red blood cell counts with a gain in number of red blood cells per cubic millimeter varying from 680,000 to 1,190,000 in different patients during the ten-day period following the administration of a large dose of liver extract. A similar satisfactory increase in the amounts of hemoglobin was also observed.

The white blood cell counts at the end of the ten-day period after liver extract administration were essentially at the same level as before treatment but under further medication increased to a normal level by the end of the period of observation in each case. Three patients showed leukocytosis during the reticulocyte response. One patient (B. P.) had an elevated white count beginning forty-eight hours after the liver extract administration which lasted for two days reaching a maximum of 14,250 per c.mm. at seventy-two hours. This period of leukocytosis accompanied the "blast crisis" described above. Patient H. R. had an elevated white blood count sixty and seventy-two hours after the administration of liver extract, the highest value being 13,200 per c.mm. In patient A. B. the white blood cell count one hundred and seventy-two hours after the administration of liver extract was 12,450 per c.mm., the leukocytosis lasting twelve hours. The fourth patient showed no elevation of the white blood cell count during the period of observation. In these patients the leukocytosis apparently developed as a part of the bone marrow response rather than as a response to infection since none showed evidence of a complicating infective process during the period of observation.

Duration of the Effect of a Single Massive Dose of Liver Extract. While a large single dose of liver extract may, as has been shown, produce a very satisfactory reticulocyte response, the effect is not lasting. After a sufficient interval of time, if more extract is given, a second reticulocyte response may be produced, the magnitude of which depends upon the time elapsing after the initial dose. Patient J. R. was given a second dose of thirty vials of liver extract seventeen days after the first had been given. A second reticulocyte response was produced, the highest percentage of the reticulocytes following the second dose of extract being 6.0 on the fifth day (Chart III).

Eight days after the second large dose of liver extract, daily doses of four vials of liver extract were given without further elevation of the reticulocyte percentage. From this evidence the effect of thirty vials of liver extract appears to persist for eight days but not for seventeen days. Patient B. P. was given the equivalent of 300 gm. of liver daily in the form of liver extract twelve days after the original dose of thirty vials of liver extract and showed a reticulocyte response with a maximum reticulocyte percentage of 5.7 on the eighth day. In this case the effect of thirty vials of liver extract lasted less than twelve days. A third patient, A. B., was given four vials of liver extract twelve days after the original dose of liver extract and showed a reticulocyte response in which the maximum reticulocyte response of 3.1 per cent was reached on the

CHART III.—DURATION OF THE EFFECT OF SINGLE DOSES OF 30 VIALS OF LIVER EXTRACT.


R.B.C. MILLIONS PER CU. MM.
RET. CELLS %
30 VIALS LIVER EXT. (ONE DOSE)
30 VIALS LIVER EXT. (ONE DOSE)
4 VIALS LIVER EXT. DAILY
R.B.C.
RET. CELLS
0 5 10 15 20 25 30 35
DAYS OF TREATMENT

eighth day. From these figures it seems probable that the effect of thirty vials of liver extract lasts in the neighborhood of ten days, the average dose being three vials of liver extract per day. This is in accordance with the findings observed when daily doses of liver extract are used, three vials per day being the minimum dose giving satisfactory results.

Summary. 1. The observed effect of single large doses of liver extract on patients with pernicious anemia confirms the opinion, expressed by Minot, that the response to liver medication depends rather on the total amount of the active liver principle used during a certain period of time rather than on the amount consumed each day. A similar effect is obtained from the thirty vials of liver extract given in a single dose or in 10 doses of three vials each at daily

intervals. The active liver principle seems to be utilized in a quantitative fashion, the effect of a given amount lasting a given time, the minimum daily amount sufficient for a satisfactory response being that present in three vials of liver extract (approximately equivalent to ½ pound of liver).

2. The magnitude of the reticulocyte response does not appear to be influenced by the presence within the body of an excessive amount of the active liver principle, a certain maximum number of reticulocytes being possible in any case, the number being related to the original blood level.

3. The rate of the reticulocyte response appears to be accelerated to a certain extent by the dosage of the liver extract, the response occurring most rapidly when a large, single dose or large daily doses of liver extract are given. When the reticulocyte response develops at a maximum rate, as it apparently does after the administration of a single dose of thirty vials of liver extract, reticulocytes begin to increase in numbers and percentage about forty-eight hours after the giving of the liver extract. A maximum number and percentage of reticulocytes appears between one hundred and four and one hundred and forty hours after the administration of liver extract and the reticulocyte response ends within two hundred and forty hours.

4. That the administration of a single dose of thirty vials of liver extract has an intensely stimulating effect upon the hematopoietic tissues of the bone marrow is indicated by the presence of numerous nucleated red blood cells and immature white blood cells of myeloid origin in the blood during the first two or three days after the liver extract is given.

5. The immediate clinical effects, reticulocyte response and increase in the red blood count and the amount of hemoglobin in the blood are as satisfactory after a single dose of thirty vials of liver extract as when three vials doses are given daily for ten days. The effect of a single dose of thirty vials lasts approximately ten days.

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ERYTHROCYTE SEDIMENTATION, PLASMA FIBRINOGEN AND LEUKOCYTOSIS AS INDICES OF RHEUMATIC INFECTION.

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The administration of salicylates to patients with rheumatic fever frequently causes prompt subsidence of the fever and polyarthritis. The occasional recrudescence of these symptoms on discontinuing medication indicates that the symptomatology rather than the underlying infection has been altered by the drugs and that these symptoms alone cannot be utilized as indices of the course of the disease. This fact frequently is overlooked, and, as a result, many patients are allowed out of bed before the infection has subsided. It is probable that such an error, in many instances, prolongs the total duration of the disease by favoring renewed activity of the infection and increases the amount of permanent cardiac damage suffered by the patient. Because of these difficulties all possible indices of the activity of the underlying infection should be investigated.

Swift, Miller and Boots[1] have directed attention to the significance of the leukocyte curve in rheumatic fever. Their studies demonstrate that, in the absence of nonrheumatic infection, a persisting leukocytosis indicates activity of the rheumatic infection. Conversely, repeated white blood cell counts below 9000 per c.mm., after the discontinuance of antirheumatic drugs, signify that the disease is nearing its end.

It is known that in rheumatic fever at the height of the disease the rate of sedimentation of the red blood cells is greatly accelerated. Herrmann,[2] in a study of 46 patients, observed that the sedimentation rate returned to normal more slowly than the temperature and leukocyte count. Kahlmeter[3] and Sharpless[4] have made similar observations, and Kahlmeter[3] has stated that the rheumatic infection cannot be considered terminated until the sedimentation rate has become normal. The work of these investigators is subject to the following criticisms: (1) None of the observers presented simultaneous measurements of the sedimentation rate and leukocyte count throughout the course of the disease. (2) In measuring the sedimentation rate the blood specimens were diluted with a solution of sodium citrate; this dilution makes accurate measurements impossible.[5] (3) No attempt was made to correct the results for variations in the cell-volume percentage of the blood specimens

employed. It is, therefore, impossible to state to what extent the rapid rate found by these investigators was due to the anemia which often accompanies rheumatic fever.

Rourke and Ernstene[6] recently reported a method by which a correction can be made for the accelerating effect of anemia on the sedimentation rate. The corrected rate (corrected sedimentation index) obtained in this manner gives more accurate information regarding the presence of infection or tissue damage in the body than do rates obtained by older methods. The present study was undertaken to learn whether the corrected sedimentation index might be a reliable criterion of the underlying activity of the infection in rheumatic fever.

The plasma fibrinogen has been shown to be increased in rheumatic fever and in all other infections in which it has been measured. It is generally accepted that there is a close relationship between the concentration of this protein and the rate of sedimentation, and it seemed desirable to ascertain whether the plasma fibrinogen content also might be a reliable index of the rheumatic infection.

Methods. Simultaneous measurements of the corrected sedimentation index, plasma fibrinogen content and leukocyte count were made at frequent intervals on 22 patients with rheumatic fever. Eleven patients had the monocyclic, 8 the polycyclic and 3 the continuous form of the disease. The periods of observation varied from three to fourteen months. Measurements usually were made every four or five days while the patients were in the hospital and subsequently at monthly intervals. The blood specimens were collected between 9 and 11 A.M. or 2 and 4 P.M. All white blood cell counts were made by one observer, using U. S. Bureau of Standards equipment, and all counts below 9000 cells per c.mm. were considered normal. The corrected sedimentation index was obtained by the method of Rourke and Ernstene.[6] With this method the upper limit of the normal rate is 0.35 mm. per minute. Plasma fibrinogen was measured by the method of Wu,[7] all analyses being done in duplicate. The upper limit of the normal plasma fibrinogen content has been placed at 320 mg. per 100 cc. In 89 measurements in this laboratory on 50 normal subjects only 2 results above this level were recorded. All patients were examined for the presence of nonrheumatic infections at the time of each series of observations to exclude extraneous influences so far as possible. Salicylates were administered to all patients during the attack.

Results. *Monocyclic Type of Rheumatic Fever.* In this type of rheumatic fever the patients have severe polyarthritis, high fever and the toxic manifestations of the disease but recover without relapse. The leukocyte count drops rapidly to normal or almost normal after the institution of antirheumatic therapy, while discontinuance of the drugs frequently is followed by a slight, tem-

porary rise in the number of white blood cells.[1] The observations on patients with monocyclic rheumatic fever in the present investigation are illustrated by the following case report:

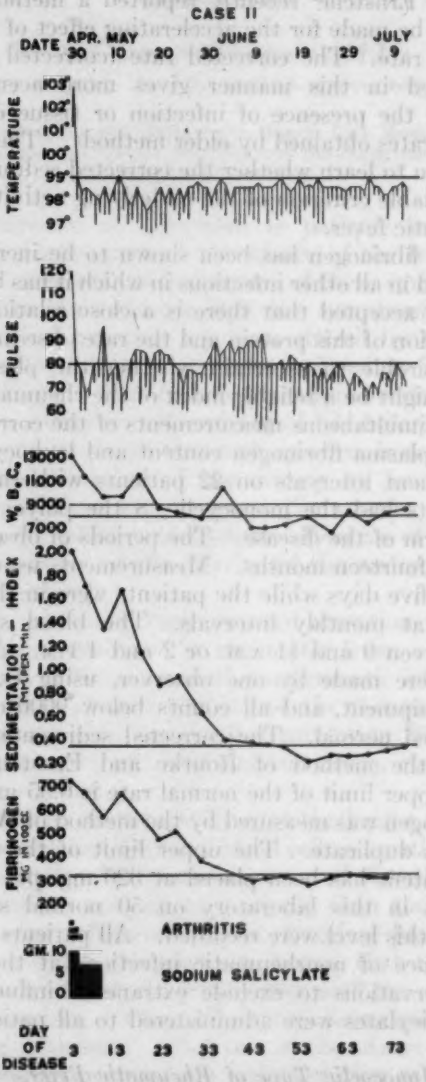

CHART 1.—Example of monocyclic type of rheumatic fever. In this and subsequent clinical charts the daily range of the temperature and pulse rate is indicated by the vertical lines in the curves for the temperature and pulse rate. Severe arthritis is represented by a heavy solid line and mild arthritis by an open dot.

Case XI (Chart 1).—T. G., a white male, aged twenty-one years, entered the hospital April 30, 1928, with severe migratory polyarthritis of two

days' duration. He had had one previous attack of rheumatic fever six years before. On admission, his temperature was 103° F. and the pulse rate 120 per minute. The heart was not enlarged. A soft systolic murmur was heard at the apex. Both ankles and the left knee were red, hot, swollen and extremely tender. The leukocyte count was 13,200 per c.mm.; the corrected sedimentation index 2 mm. per minute; and the plasma fibrinogram 721 mg. per 100 cc. All symptoms diminished rapidly with sodium salicylate therapy. On the day after admission to the hospital the temperature did not exceed 99° F., and it did not again rise above this level except on the thirteenth day of the disease. With the disappearance of symptoms, the leukocyte count, corrected sedimentation index and plasma fibrinogen content decreased rapidly, although the abrupt discontinuance of sodium salicylate at the end of the ninth day of illness was followed by a temporary intermediate rise in all three. The white blood cell count reached 8600 per c.mm. on the twenty-second day of the disease, while a normal corrected sedimentation index and plasma fibrinogen content were not recorded until the forty-fifth and forty-second days respectively.

DURATION OF SIGNS OF INFECTION IN RHEUMATIC FEVER.

Case No.	Type of rheumatic fever.	Temperature above 99° F. (days).	Pulse-rate above 80 per minute (days).	Arthritis (days).	Leukocyte count above 9000 per c.mm. (days).	Sedimentation index above 0.35 per minute (days).	Plasma fibrinogen above 320 mg. per 100 cc. (days).	Salicylates last given (day of disease).
11	Monocyclic	3	51	5	21	44	41	9
3	Monocyclic	4	4	5	24	31	35	16
20	Monocyclic	5	6	7	9	15	15	12
4	Monocyclic	6	49	30	43	61	66	18
17	Monocyclic	7	6	9	21	31	31	23
14	Monocyclic	7	23	13	26	47	52	18
15	Monocyclic	7	13	6	22	25	29	8
16	Monocyclic	8	27	6	8	14	14	18
5	Monocyclic	9	15	11	12	77	77	80
7	Monocyclic	17	34	9	18	37	51*	23
22	Monocyclic	21	8	10	26	54	54	24
1	Polycyclic	20	31	19	23	46	‡	17
9	Polycyclic	26	46	28	51	57	63	42
12	Polycyclic	36	106*	38	54	49	54	58
8	Polycyclic	37	182*	37	101	82	115*	52
19	Polycyclic	55	57	68	122	122	150*	78
2	Polycyclic	76	343*	72	107	138*	‡	89
21	Polycyclic	83	116	23	88	88	88	42
13	Polycyclic	85	223*	98	133	161	188*	109
18	Continuous	61	416†	57	416†	416†	416†	88
6	Continuous	75	342*	62	105	203*	182*	94
10	Continuous	192*	326†	326†	192*	326†	326†	247

* Indicates normal value first recorded at "follow-up" examination.
† Indicates result above normal value at time of last observation.
‡ Not measured.

A summary of the studies on the 11 patients with the monocyclic type of rheumatic fever is included in the table. This shows that the leukocyte count usually returned to a level below 9000 per c.mm. within a few days to two weeks after the subsidence of fever

and polyarthritis. The corrected sedimentation index did not return to normal until the white blood cell count had been below 9000 per c.mm. for a period varying from a few days to about two months. The plasma fibrinogen usually reached a normal value at approximately the same time as the corrected sedimentation index, although in 1 of the 11 patients it remained elevated for a considerably longer time. The temperature usually became normal before the pulse rate, and at times an elevated pulse rate persisted after the leukocyte count, corrected sedimentation index and plasma fibrinogen content had become normal.

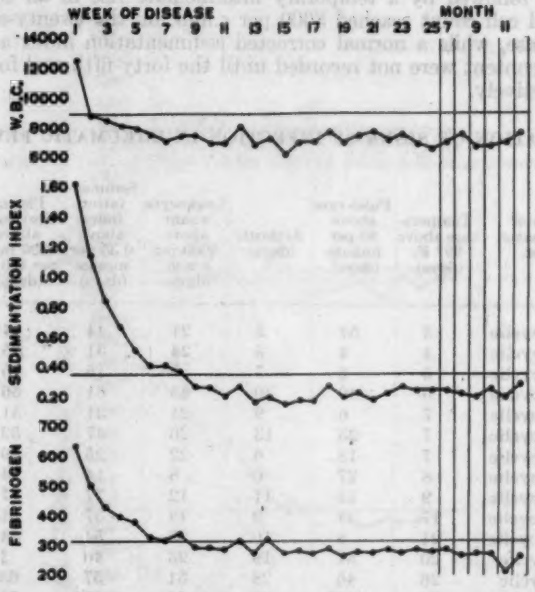

CHART 2.—Curves of the average leukocyte count, corrected sedimentation index, and plasma fibrinogen content in monocyclic rheumatic fever.

Curves of the average leukocyte count, corrected sedimentation index and plasma fibrinogen content of the patients with monocyclic rheumatic fever are given in Chart 2. During the first week of the disease there was an abrupt fall toward normal in all 3 averages, but especially in the leukocyte curve. After the fourth week of the disease the average leukocyte count was 8000 per c.mm. or less. The corrected sedimentation index and plasma fibrinogen content, however, did not become and remain normal until the ninth week of the disease.

Polycyclic Type of Rheumatic Fever. This type of rheumatic fever is characterized by the occurrence of one or more relapses of fever, tachycardia and polyarthritis after the initial subsidence of these

symptoms. The leukocyte count tends to remain above the normal level between relapses.[1] After the last relapse the count falls gradually to normal. The results obtained on patients with this type of rheumatic fever in the present investigation are exemplified by the following case report:

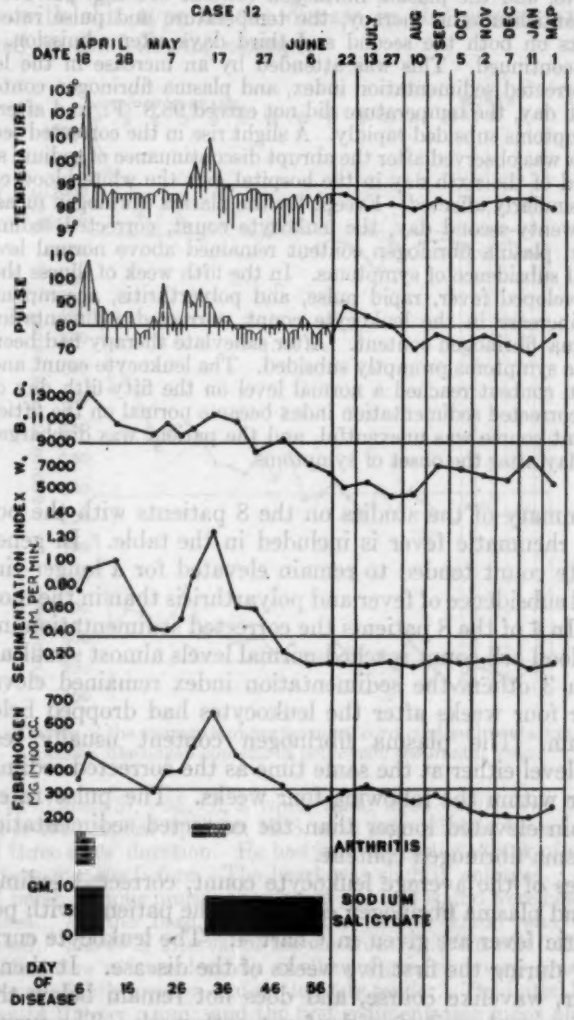

CHART 3.—Example of polycyclic type of rheumatic fever. The observations enclosed by the vertical lines on the right side of the chart were made at follow-up examinations.

CASE XII (Chart 3).—C. H., a white male, aged twenty-eight years, entered the hospital on the night of April 17, 1928, with severe polyarthritis, high fever, and tachycardia of five days' duration. There had been no

previous attacks of rheumatic fever. The heart was not enlarged. There was a soft, blowing systolic murmur at the apex. The right knee and right ankle were swollen, red, hot and extremely tender. The left knee, left ankle and right wrist were similarly but less severely involved. Salicylate therapy was instituted immediately. On the following day the leukocyte count was 12,100 per c.mm., the corrected sedimentation index 0.75 mm. per minute, and the plasma fibrinogen content 375 mg. per 100 cc. In spite of antirheumatic therapy, the temperature and pulse rate reached new peaks on both the second and third days after admission, and the arthritis continued. This was attended by an increase in the leukocyte count, corrected sedimentation index, and plasma fibrinogen content. On the fourth day, the temperature did not exceed 98.8° F., and after this the other symptoms subsided rapidly. A slight rise in the corrected sedimentation index was observed after the abrupt discontinuance of sodium salicylate at the end of the sixth day in the hospital, but the white blood cell count was not similarly affected. Except for the plasma fibrinogen measurement on the twenty-second day, the leukocyte count, corrected sedimentation index and plasma fibrinogen content remained above normal levels after the initial subsidence of symptoms. In the fifth week of illness the patient again developed fever, rapid pulse, and polyarthritis, accompanied by a decided increase in the leukocyte count, corrected sedimentation index, and plasma fibrinogen content. After salicylate therapy had been reinstituted, the symptoms promptly subsided. The leukocyte count and plasma fibrinogen content reached a normal level on the fifty-fifth day of illness, and the corrected sedimentation index became normal on the fiftieth. The subsequent course was uneventful, and the patient was discharged on the sixtieth day after the onset of symptoms.

A summary of the studies on the 8 patients with the polycyclic type of rheumatic fever is included in the table. In general, the leukocyte count tended to remain elevated for a longer time after the final subsidence of fever and polyarthritis than in the monocyclic form. In 4 of the 8 patients the corrected sedimentation index and white blood cell count reached normal levels almost simultaneously, while in 3 others the sedimentation index remained elevated for three or four weeks after the leukocytes had dropped below 9000 per c.mm. The plasma fibrinogen content usually reached a normal level either at the same time as the corrected sedimentation index or within the following four weeks. The pulse rate tended to remain elevated longer than the corrected sedimentation index and plasma fibrinogen content.

Curves of the average leukocyte count, corrected sedimentation index and plasma fibrinogen content in the patients with polycyclic rheumatic fever are given in Chart 4. The leukocyte curve drops steadily during the first five weeks of the disease. It then runs an irregular, wavelike course, and does not remain below the upper limit of normal until after the fourteenth week. The curves of the average corrected sedimentation index and plasma fibrinogen content roughly parallel that of the average leukocyte count but do not remain within normal limits until after the twenty-second week.

Continuous Type of Rheumatic Fever. In this form of the disease tachycardia and intermittent elevations of temperature persist for

a long period, and cardiac involvement is an outstanding feature. Recurring attacks of polyarthritis, although common, are a less prominent part of the clinical picture. In children subcutaneous nodules frequently are present. The white blood cell count is not appreciably affected by antirheumatic therapy and remains elevated as long as the infection continues active.[1] The results obtained on patients with this type of the disease in the present study are illustrated by the following example:

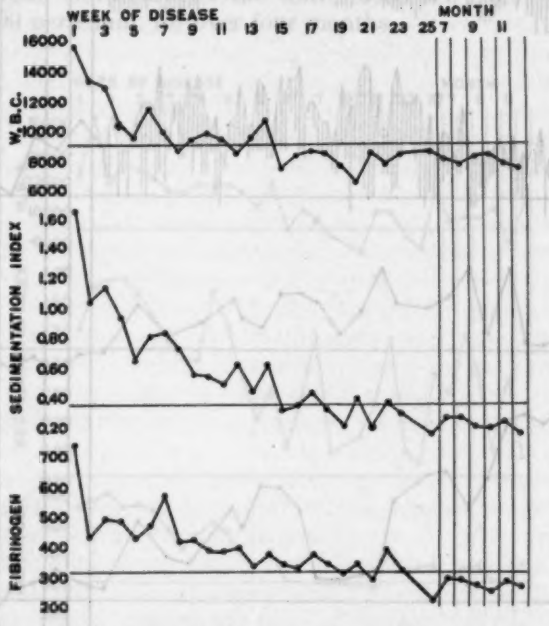

CHART 4.—Curves of the average leukocyte count, corrected sedimentation index, and plasma fibrinogen content in polycyclic rheumatic fever.

CASE VI (Chart 5).—M. C., a white male, aged twenty-two years, was admitted to the hospital April 30, 1928, with polyarthritis, fever and tachycardia of three days' duration. He had had one earlier attack of rheumatic fever sixteen months before. The heart was slightly enlarged. A presystolic and harsh systolic murmur replacing the first sound were heard at the mitral area. At the base the pulmonic second sound was decidedly accentuated. The *P–R* interval of the electrocardiogram was 0.22 seconds. Both ankles were red, moderately swollen, warm, and very tender. The left knee was slightly swollen and moderately tender. The initial leukocyte count was 14,100 per c.mm., and the first sedimentation index and plasma fibrinogen values were distinctly elevated. The patient remained in the hospital for three and a half months, during which time there were several temporary slight elevations of temperature. The tachycardia persisted and at irregular intervals became much more pronounced; this rapid pulse-rate, in fact, constituted the principle symptom of the infection. Three courses of sodium salicylate were given. The leukocyte curve followed a

wavelike course and did not fall below 9000 per c.mm. until the one hundred and sixth day of illness. The curve of the sedimentation index followed a more distinctly downward course in the first half of the period of hospitalization; but in the ninth week of the disease it increased markedly and did

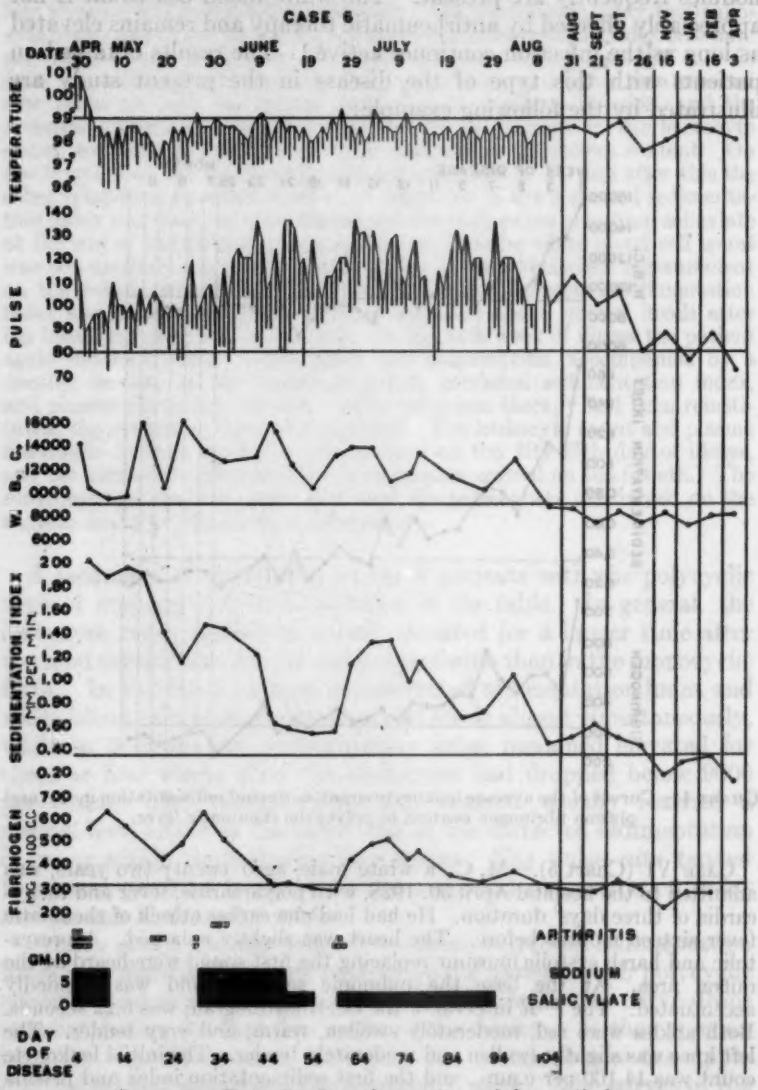

CHART 5.—Example of continuous type of rheumatic fever.

not become normal until the leukocyte count had been below 9000 per c.mm. for three months. The plasma fibrinogen curve roughly paralleled that of the sedimentation index, although it reached a normal level a few weeks earlier than the latter.

A summary of the studies on the 3 patients with the continuous type of rheumatic fever is included in the table. In 1 patient the pulse rate, corrected sedimentation index, plasma fibrinogen content and leukocyte count were still above normal fourteen months after the onset of the illness. In another the plasma fibrinogen remained elevated for two and a half months and the sedimentation index for over three months after the leukocyte count had become normal. In the third the pulse rate, sedimentation index and plasma fibrinogen were still elevated after the white blood cell count had been below 9000 per c.mm. for over four months.

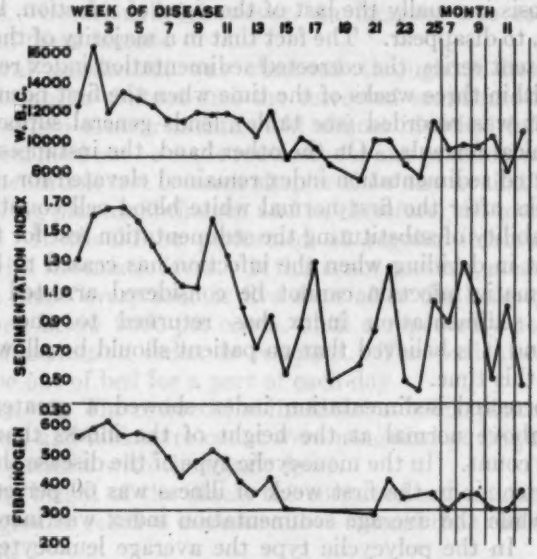

CHART 6.—Curves of the average leukocyte count, corrected sedimentation index, and plasma fibrinogen content in the continuous form of rheumatic fever.

Curves of the average white blood cell count, corrected sedimentation index and plasma fibrinogen content in the patients with the continuous type of rheumatic fever are presented in Chart 6. The small number of cases studied introduces a large error in these averages. Each curve, however, follows an irregular, gradually downward course, and in the twelfth month of the disease none had yet reached a normal level.

Discussion. The results of the present investigation indicate that the corrected sedimentation index is a more sensitive criterion of activity of the infection in rheumatic fever than the leukocyte count. In all types of the disease the sedimentation rate, with few exceptions, remained elevated for several days to a few weeks after the white blood cell count had become normal. Had there been a

constant interval between the times when the two measurements reached normal it might have been assumed that the persistent elevation of the sedimentation rate was only a residual manifestation of a preceding systemic reaction. The fact that this period was variable, however, indicates with great probability that such was not the case and that the elevation of the corrected sedimentation index was due to persistent low-grade rheumatic infection. It is a widely accepted rule that no patient with rheumatic fever should be allowed out of bed until he has been free of all symptoms and signs of the infection for two or three weeks, during which time he should not have been receiving antirheumatic drugs. Leukocytosis is usually the last of the signs of infection, heretofore employed, to disappear. The fact that in a majority of the patients in the present series, the corrected sedimentation index returned to normal within three weeks of the time when the first normal leukocyte count was recorded (see table), lends general support to the above clinical formula. On the other hand, the instances in which the corrected sedimentation index remained elevated for more than three weeks after the first normal white blood cell count, indicate the advisability of substituting the sedimentation test for the leukocyte count in deciding when the infection has ceased to be active. The rheumatic infection cannot be considered arrested until the corrected sedimentation index has returned to and remained normal, and it is believed that no patient should be allowed out of bed until this time.

The corrected sedimentation index showed a greater relative increase above normal at the height of the illness than did the leukocyte count. In the monocyclic type of the disease the average leukocyte count in the first week of illness was 60 per cent above normal, while the average sedimentation index was increased 360 per cent. In the polycyclic type the average leukocyte count in the first week of the disease was 85 per cent above normal, while the corrected sedimentation index was increased 370 per cent. In the continuous type the maximum average leukocyte count was 94 per cent above normal, while the corresponding average of the corrected sedimentation index was 360 per cent above normal. Exacerbations of the infection in the polycyclic and continuous types of the disease were preceded or accompanied by distinct increases in both the leukocyte count and corrected sedimentation index, but the rise in the sedimentation index usually was of much greater relative extent than the increase in the number of white blood cells. These observations suggest that the corrected sedimentation index is a more sensitive indicator of the infection than the leukocyte count.

There was evidence that both the leukocyte count and the corrected sedimentation index were depressed by antirheumatic drugs; but, in general, the sedimentation index seemed to be less affected in this way than the white blood cell count. The subsidence of

symptoms under salicylate therapy usually was accompanied by a pronounced drop toward normal in both measurements. In the monocyclic type of the infection the leukocyte count occasionally reached a normal level at this time, but in no instance was such a profound depression of the corrected sedimentation index observed. In patients with the polycyclic or continuous type of the disease the leukocyte count and corrected sedimentation index remained above normal between exacerbations of the infection, even though salicylate therapy was continued without interruption. In all types of the disease a slight increase in the white blood cell count and corrected sedimentation index followed by a prompt return to the previous level frequently was observed after discontinuance of salicylates. Occasionally, however, an increase was recorded in only one of these factors.

A general parallelism was observed throughout between the plasma fibrinogen content and the corrected sedimentation index. Since these two measurements yield almost identical information, both of them need not be made routinely for any practical advantage. The sedimentation test is much simpler than any available method for measuring plasma fibrinogen and is, therefore, the measurement of choice. It should be performed at regular intervals on all patients with rheumatic fever. If this is not possible, measurements should be made every four or five days after the leukocyte count has dropped below 9000 per c.mm. until a repeatedly normal corrected sedimentation index is recorded. The patient may then begin to be out of bed for a part of each day.

Summary. 1. The corrected sedimentation index, plasma fibrinogen content, and leukocyte count were measured at frequent intervals in 22 patients with rheumatic fever.

2. At the height of the illness the corrected sedimentation index showed a greater relative increase above normal than did the leukocyte count.

3. Both the leukocyte count and the corrected sedimentation index were depressed somewhat by salicylates, but, in general, the sedimentation index seemed to be less affected than the white blood cell count.

4. A slight increase in the leukocyte count and corrected sedimentation index followed by a prompt return to the previous level was observed frequently after discontinuance of salicylates.

5. With exacerbations of the infection in the polycyclic and continuous types of the disease, there was usually a greater relative increase in the corrected sedimentation index than in the leukocyte count.

6. In all types of the disease the corrected sedimentation index, with few exceptions, remained elevated for several days to a few weeks after the leukocyte count had become normal.

7. A general parallelism was observed throughout the course of

the disease between the plasma fibrinogen content and the corrected sedimentation index.

8. The observations indicate that the corrected sedimentation index and plasma fibrinogen content furnish almost identical information and are more accurate indices of the infection in rheumatic fever than the leukocyte count. The corrected sedimentation index is the preferable clinical test on account of its greater simplicity. The infection cannot be considered arrested until the corrected sedimentation index has become and remained normal.

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THE VALUE OF BLOOD BILIRUBIN ESTIMATIONS IN THE DIFFERENTIAL DIAGNOSIS OF CEREBROVASCULAR ACCIDENTS.

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A paresis or paralysis of any part of the body, most often a hemiplegia, more or less sudden in onset, and dependent on a disturbed circulation, may be classed as a cerebrovascular accident. The condition is commonly described as "a stroke," or apoplexy, where apoplexy is used in its original meaning of being struck down, rather than being confined to hemorrhagic conditions. Pathologically such an accident is due to thrombosis of a bloodvessel, a hemorrhage, or an embolus lodged within the vessel. Cerebrovascular spasm or a slowing of the blood stream due to a fall in blood pressure might also be included. The clinical picture has been well recognized since the time of Charcot, and little has developed since that time to distinguish the kind of process producing the paralysis. One is struck by the lack of uniform opinion

as to the relative incidence of such common lesions and by the clinician's inability in the majority of cases to make an accurate diagnosis. Certain findings have been described which may be taken as the basis for a reasonably certain diagnosis, but after assembling all the data available it is often impossible to come to a decided conclusion. As the treatment of a case of cerebral thrombosis may be diametrically opposed to the treatment of a case of hemorrhage, any diagnostic procedure which may assist in distinguishing the nature of the lesion would be of great value. In 1928 Wilder[1] showed that studies of the blood serum bilirubin content might be relied upon to give the correct diagnosis in most cases.

Blood Bilirubin Tests. There are two outstanding methods for determining blood serum bilirubin content: The icteric index and the Van den Bergh reactions. The technique of both is described in most books on clinical pathology. The first is a simple quantitative measurement by an arbitrary standard. Average normal values range between 3 and 7 units. The second is both a quantitative and qualitative test. The first part of the test is called the immediate direct reaction. It is only positive when the source of the bilirubin increase is in the liver and biliary tract, and is always negative when the pigment increase is hematogenous in origin. The second part of the test is a quantitative measure of the pigment by degree of dilution. It is recorded in both units and in milligrams per 100 cc. of blood. Normal figures are 0.2 to 0.4 units or 0.5 to 2 mg.

Originally the two reactions were thought to depend on a difference between the bilirubin formed from bile pigment and that formed from blood pigment which would distinguish the source of a disordered pigment metabolism. Blankenhorn[2] and others now feel that the difference in the reactions is due to the rate of absorbtion of the pigment into the blood stream. When it is absorbed slowly, as is usual in hematogenous icterus, it is combined with protein and gives only the indirect reaction. When it enters the blood stream rapidly, as in obstructive icterus, no such combination takes place and the direct reaction occurs. Combined and uncombined bilirubin in excess may both be present, giving the so-called delayed direct and biphasic reactions. The interpretation of these is difficult clinically and has given rise to considerable criticism of the original claims for the test.

As quantitative tests, both the icterus index and the Van den Bergh tests are reliable in measuring the degree of jaundice barring technical errors, and represent one of the recent really important advances in clinical pathology. Qualitatively, if the direct Van den Bergh reaction is negative an increase in blood bilirubin is considered as very probably hematogenous in origin, and if the direct reaction is positive there is some disturbance in bile pigment

metabolism. In clear-cut reactions then the Van den Bergh test can be used to demonstrate a hematogenous cause for an increase in blood serum pigment.

Relation of Bilirubin Tests to Apoplexy. The application of these tests to the differential diagnosis of cerebrovascular accidents has already been attempted by Wilder[1] in Vienna. In a cerebral hemorrhage the extravasated blood is in an enclosed space, and the blood pigment will be gradually absorbed from the affected area and transported by the blood stream elsewhere. As this does not occur to any degree in cerebral softening, evidence of the absorbed pigment in the blood serum might serve to distinguish the two types of brain lesions one from the other. There are three questions of prime importance to be considered: (1) Are all cerebral hemorrhages large enough to give definite symptoms, sufficiently large to cause an increase in serum bilirubin content? (2) In large areas of so-called red softening is there sufficient blood extravasated to affect the normal icteric index? (3) If a cerebral hemorrhage constantly raises the icteric index does it do so early enough to be of any practical clinical value? Only a careful study of a large series of cases can answer these questions.

Wilder's report on the subject is the only one which has appeared in the available literature to date, and it seems strange that a problem which may offer so much has been so neglected. This author presented two groups of cases of cerebral hemorrhage. One was confirmed by postmortem examination, and in the other the clinical diagnosis was practically certain. Blood bilirubin was measured by dilution ratios, and the icteric index and qualitative Van den Bergh reactions were not reported. In the first group there were 8 cases tested within six days after the accident. All but one showed a clear-cut increase in serum bilirubin. The exception was only a cherry-sized hemorrhage tested one day after onset, and it had broken into the ventricle. Two of the cases showed the increase one day after the insult. In the second group there were 5 cases which included a meningeal hemorrhage, an abscess hematoma, two brain tumors and a case with obscure test findings. The first 4 showed a marked increase in blood bilirubin, 2 after the first day. However, one test showed the increase after twenty-seven days. Two other hemorrhage cases showed normal values after thirty-five days and sixty days. Five out of 6 cases with normal serum dilution values showed softening at autopsy, the sixth had icterus and gall stones. In 25 other cases thought to be softening, all but 3 gave normal values, the exceptions were not proven not to have bled. Tests on 8 other cases of miscellaneous nonhemorrhagic cerebral disorders showed no tendency toward icterus.

Wilder concluded that one could determine with a very great probability whether an apoplectic insult was due to hemorrhage or not. The bilirubin is increased within the first twenty-four hours

and may remain up for four weeks. Consequently the test is extremely important in differential diagnosis. The author was handicapped in some of his cases by not being able to distinguish between icterus of hepatogenous and hematogenous origin.

Present Series. In the 50 cases of cerebrovascular accident which compose the present series the blood bilirubin was estimated from one day to three months after the ictus. Of this number 11 died, but autopsies were obtained on only 5 cases. Although there is a postmortem confirmation of the diagnosis in so few instances, the results of the bilirubin tests seem to bear important relationships to the clinical findings. The cases have been divided up into groups according to whether they showed positive, negative or doubtful tests. As with many laboratory tests, it is difficult to establish a clear-cut division between normal and abnormal readings. The normal range of the icterus index values has been taken as from 4 to 7 units inclusive. A reading of 8 units, although often accepted as a definite increase, has been regarded as a borderline reading. The normal quantitative Van den Bergh readings are 0.2 to 0.4 units; anything over 0.4 is judged an increase. Twenty cases showed an increase in serum pigment. Three of these were discarded as the direct Van den Bergh was positive, indicating a biliary tract pigment metabolism disturbance, which would obscure any changes due to hematogenous causes. Ten cases gave normal bilirubin values, and 5 more were in the borderline group. In the remaining 15 cases there was insufficient data to warrant their inclusion.

In the 17 cases with a clear-cut increase in the icterus index and a negative direct Van den Bergh reaction there is considerable lack of correlation between the clinical findings and those of the tests. (Table I.) Although the clinical diagnosis was frequently in doubt, an impression was usually expressed, based upon the symptomatology and findings. All types of onset occurred and many of the patients were not comatose. Some had had previous attacks. Although the blood bilirubin tests would indicate that all suffered from cerebral hemorrhage, the following clinical impressions were recorded in the 17 histories. Six were thought to have hemorrhage, 8 thrombosis (including 3 syphilitics), 1 trauma and 2 uremia. Only 5 of these 17 cases died while in the hospital. One, the trauma case, showed at autopsy, a fractured skull, which had been undiagnosed by Roentgen ray, and a large subdural hemorrhage. Of the remaining 4 deaths, 2 came to autopsy and in both the clinical diagnosis of uremia was confirmed. Both showed multiple small brain hemorrhages. In the other 2 cases 1 was thought to be hemorrhage, the other thrombosis. Thus, 9 of the 17 showed some evidence of hemorrhage.

Controversial findings also exist in those cases with normal serum bilirubin values but to a lesser degree. The tests should indicate

that no hemorrhage has occurred. The clinical impressions in this group of 10 cases (Table II) were: hemorrhage, 2; thrombosis, 7 (including 1 case of syphilis and 1 case of probable cerebral embolus); trauma, 1. Three of these patients died, including the one suspected of embolus, but no autopsies were held. There were 2 cases of thrombosis in the original series which came to anatomical examination, both of whom had positive direct Van den Bergh tests. Such findings emphasize the importance of the qualitative Van den Bergh findings in these tests.

TABLE I.—CASES OF CEREBROVASCULAR ACCIDENT WITH INCREASED BLOOD BILIRUBIN.

Case No.	Interval before tests.	Icterus index.	Van den Bergh reaction.		Clinical impression.	Remarks.
			Direct.	Indirect.		
3	3 mos.	11.5	Neg.	0.50	Hemiplegia; thrombosis	Died; urinary tract infection.
4	2 "	13.4	Neg.	0.70	Paresis with hemiplegia	Malaria; fair recovery.
5	7 days	14.0	Neg.	0.60	Hemiplegia; thrombosis	Spastic paralysis.
8	4 "	14.0	Neg.	0.50	Hemiplegia; thrombosis	Attacks of syncope.
9	10 "	11.0	Neg.	...	Hemiplegia thrombosis	Hypertension; one previous "stroke."
10	5 "	12.0	Neg.	0.80	Uremia with hemiparesis	Autopsy; multiple small cerebral hemorrhages.
14	5 "	12.0	Neg.	0.80	Cerebrovascular syphilis with hemiplegia	Previous attack.
19	6 "	9.2	...	...	Hemiplegia hemorrhage	Died.
31	7 "	15.0	...	...	Skull fracture	Autopsy: skull fracture (not seen in Roentgen ray) and large subdural hemorrhage.
32	"Sometime ago"	14.0	Neg.	0.85	Hemiplegia thrombosis	Had five "strokes."
34	2 mos.	15.8	Neg.	0.7	Hemiplegia; hemorrhage	Hypertension; good recovery.
37	7 days	12.0	...	...	Cerebrovascular syphilis with hemiplegia	
42	1 mo.	9.0	Neg.	...	Hemorrhage	Hypertension; fair recovery.
43	2 days	12.0	Neg.	...	Uremia with convulsive seizures	Autopsy: glomerular nephritis; multiple small brain hemorrhages.
45	8 "	10.0	...	...	Hemorrhage	
46	14 "	13.0	...	...	Hemorrhage	
48	3 "	27.0	...	...	Hemorrhage	

In the 5 cases with borderline bilirubin values (Table III) only 2 had Van den Bergh reactions done on them. The blood was tested on all of them between seven and twenty-six days after the

ictus. Three were thought to be thrombosis, and these cases might represent the so-called "red softening" where some hemorrhage has taken place into the infarcted area. One case was diagnosed encephalitis, and one case simply cerebrovascular accident. One case thought to be thrombosis died, but there was no autopsy.

TABLE II.—CASES OF CEREBROVASCULAR ACCIDENT WITH NORMAL BLOOD BILIRUBIN.

Case No.	Interval before tests.	Icterus index.	Van den Bergh reaction.		Clinical impression.	Remarks.
			Direct.	Indirect.		
6	36 hrs.	7.0	Neg.	0.3	Hemorrhage	Died; extreme hypertension.
17	7 days	7.5	Neg.	0.2	Hemiplegia; embolus	Died; had quinidin.
22	3 mos.	7.5	...	0.3	Hemiplegia; cerebrovascular syphilis	Malaria; fair recovery.
23	5 days	6.0	...	...	Hemiparesis; hemorrhage	Died; bronchopneumonia.
27	2 mos.	7.3	...	...	Hemiplegia; thrombosis	Previous attack.
28	1 mo.	4.2	...	...	Hemiplegia; thrombosis	Hypertension.
36	3 days	6.0	...	...	Hemiplegia; thrombosis	Three previous "strokes."
40	13 "	6.0	Neg.	...	Hemiplegia; thrombosis.	
44	1 mo.	6.0	Neg.	...	Monoplegia; thrombosis	Good recovery.
50	7 days	6.0	Neg.	...	Head trauma	Good recovery.

TABLE III.—CASES OF CEREBROVASCULAR ACCIDENT WITH INDEFINITE INCREASE IN BLOOD BILIRUBIN.

Case No.	Interval before tests.	Icterus Index.	Van den Bergh reaction.		Clinical impression.	Remarks.
			Direct.	Indirect.		
15	7 days	8.0	...	...	Hemiparesis; thrombosis.	
16	10 "	8.0	Neg.	...	Hemiplegia; thrombosis	Died of subsequent "stroke."
20	10 "	8.3	Neg.	0.4	Cerebrovascular accident	Good recovery.
26	26 "	8.7	Neg.	0.5	Hemiplegia; thrombosis	Previous attack.
49	14 "	8.0	...	...	Epidemic encephalitis	Good recovery.

Eight cases of the 35 had positive blood Wassermanns and other evidence of syphilis. Most textbooks state that hemiplegias in syphilis are due to thrombosis. As this type of cerebrovascular

accident responds to antiluetic therapy, as a rule, anatomic examinations are rarely possible. Ophüls[3] records 2 in which hemorrhages were found. This question of the exact nature of the lesion in luetic paralyses is a very important one as the tests would indicate that it is a hemorrhage, despite all the clinical impressions to the contrary. In 6 of the 8 cases the icterus index ranged between 11 and 14 units, although 1 of these showed a delayed direct Van den Bergh reaction three months after the accident. The tests were made on the other 5, five to ten days after onset, except in a case of paresis which showed a positive test after eight weeks. The 2 cases which did not show a definite increase in serum pigment were both only weakly positive in their Wassermann reactions. One of these was in an old man with marked arteriosclerosis and hypertension, and in the other the test was made three months after the onset of the paralysis.

In most instances the blood pigment tests were made within two weeks after the onset of the cerebral accident, but this was not always possible, and in 7 cases the time interval was from one to three months. As far as our present knowledge goes probably no conclusions can be drawn from normal values obtained after the first four weeks. However, four positive readings were obtained in these 7 cases, and should be indicative of hemorrhage with as yet incomplete absorption of pigment from the old blood clot.

It is also interesting to note that in this series of cases there was no constant relationship between blood pressure readings and the type of lesion indicated. Many cases of high blood pressure clinically and serologically seemed to be thrombosis, while several cases with low blood pressure were evidently hemorrhage. Both types of blood pressure were encountered after the cerebrovascular accident.

Conclusion. On the basis of Wilder's work and the cases herein reported, it seems justifiable to conclude that a definite increase in the icteric index with a negative direct Van den Bergh reaction following a cerebrovascular accident usually indicates that a hemorrhage has occurred, and that a normal index after the first day, but within the first few weeks, is strong evidence against a hemorrhage. If these conclusions are borne out by other workers in larger series of cases where autopsies are obtained estimations of serum bilirubin will present a most important basis for the differential diagnosis of the lesions.

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THE PROGNOSTIC VALUE OF THE INITIAL LEUKOCYTE AND DIFFERENTIAL COUNT IN LOBAR PNEUMONIA.

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Although clinical methods of examination of the blood are fairly well standardized, there is still no lack of interest in efforts to devise means of obtaining additional diagnostic and prognostic information from the procedure. The stained blood smear has offered a fertile field for careful investigation, and numerous methods of getting prognostic data from the differential leukocyte count have been introduced. Most of these, while admittedly based on sound premises, have the disadvantage of being complex or costly in time and have not been widely adopted. A determination of the complete Arneth index, to cite the most widely known example, requires forty-five minutes of an expert worker's[1] time and even the modified simpler form of Arneth count which has been used more recently consumes twenty minutes and calls for practiced nicety of judgment in distinguishing small variations in shape and number of segments among the nuclei of the leukocytes.

Weiss[1] and Reznikoff[2] have described Schilling's valuable simplified method of gauging the severity of infectious toxic states. It consists essentially in subdividing the polymorphonuclear leukocytes into two groups—young and adult, or unsegmented and segmented— and determining the percentage of each. They lay much less stress, however, on the individual count than on the trend of a series of counts taken at fairly short intervals. A high and increasing percentage of immature polymorphonuclear leukocytes indicates a grave illness, while a low or diminishing number foreshadows recovery.

Hinkleman[3] has pointed out the prognostic value of the determination of the absolute number of the various types of leukocytes per cubic millimeter of blood. He has formulated the following surgical prognostic rules: "(1) So long as all the cells commonly represented in the white count are present in normal absolute numbers, the patient's condition is good and the prognosis can be counted favorable. . . . (3) When the small lymphocytes begin to fall below normal absolute numbers, this marks the real beginning of disorganization of Nature's fighting force and the point at which the case should always receive a serious consideration. There is still a chance of recovery, depending on how quickly and thoroughly the cause can be removed." Todd and Sanford[4] give

the normal range of polymorphonuclear leukocytes as 3000 to 7000 per c.mm. and of lymphocytes, 1200 to 3000 per c.mm.

Suppression of the absolute number of lymphocytes usually carries with it as a correlative an undue increase in the percentage of other forms, chiefly polymorphonuclears. Since Sondern's[5] contribution, an increase in the polymorphonuclear leukocyte percentage out of proportion to the increase in total count has been repeatedly recognized as indicative of severe infection or low resistance. Gibson[6] devised a useful chart to portray by the slant of a line the proportion or disproportion between total increase and polymorphonuclear increase. A glance at such a chart gives a good idea of the danger one's patient is in. The inconvenience of dependence on a chart has caused Walker[7] to construct a simple formula which gives the same information in the form of a numeral which he has designated the "Index of Resistance." Walker's formula is as follows:

$$IR = (T-10) - (P-70).$$

In this formula IR is the index of resistance, T, the total leukocyte count expressed in thousands, and P, the polymorphonuclear leukocyte percentage. Disproportionately rapid rise in the percentage of polymorphonuclear leukocytes results in a negative value when this formula is applied. It is to be noted that Walker's formula reveals his choice of 70 per cent as the upper limit for polymorphonuclears in the normal differential count, in contrast to Gibson's original figure of 75 per cent.

Owing to the rush of work in the ordinary general hospital, it is evident that any laboratory method of prognosing the outcome of acute infectious diseases which depends on observing the trend of a series of differential counts taken at short intervals is not likely to find wide adoption. The average patient will probably receive little more than an initial complete count including smear for diagnostic purposes, supplemented by such leukocyte counts as seem called for by the progress of the disease. For this reason, we have recently interested ourselves in the question of the prognostic significance of the admission blood counts taken by interns at the Pennsylvania Hospital on patients admitted to the medical services of Dr. George W. Norris and Dr. Thomas McCrae. Lobar pneumonia was selected as the disease par excellence for this purpose because of its acuteness, severity, ease of clinical recognition and nonspecific blood picture, which apparently may serve as a type for a large number of acute infectious processes.

Does a single, frequently very early, complete blood count enable one to tell how "hard hit" a patient is with pneumonia and to estimate the outcome with any degree of accuracy? In an attempt to answer this question we have reviewed the records of 100 patients who recovered from lobar pneumonia and 60 who died of the disease. There was no selection of cases except that only frank lobar pneu-

monia was accepted. A large majority of the patients were adults, this being a general hospital with no pediatric beds.

In Table I we have tabulated side by side the total leukocytic response to the disease of the two groups of patients. Accepting 5000 to 10,000 as the normal range of leukocytes, it will be seen that among the patients who recovered there was not a single leukopenia, whereas among the fatal cases 10 per cent exhibited leukopenia. Nine per cent of those who recovered and 30 per cent of those who died had no leukocytosis. Forty-seven per cent of the patients who recovered had leukocyte counts above 20,000; only 16 per cent of the fatal cases had counts this high. These figures decisively con-

TABLE I.—TOTAL LEUKOCYTIC RESPONSE OF 100 NON-FATAL AND 60 FATAL CASES OF LOBAR PNEUMONIA.

	Recovered.		Died.	
Leukocyte count.	Number.	Per cent.	Number.	Per cent.
Below 5,000	0	0	6	10
5,000 to 10,000	9	9	12	20
10,000 to 15,000	15	15	16	27
15,000 to 20,000	29	29	16	27
20,000 to 30,000	33	33	8	13
Above 30,000	14	14	2	3
Total	100	100	60	100

firm the ominous significance of leukopenia in pneumonia and the favorable portent of high leukocytosis. The average leukocyte count of those who recovered was 21,046, and of those who died, 14,700.

The average absolute number of polymorphonuclear leukocytes per cubic millimeter among the patients who recovered as 18,130 and of lymphocytes 2159, as compared with an average of 12,711 polymorphonuclears and 1437 lymphocytes among those who died. Nineteen per cent of the patients who recovered and 52 per cent of those who died had absolute lymphocyte counts of less than 1200 per c.mm. Thus it would appear that a lymphocyte count below the low normal absolute number is often of grave significance, while a normal or higher count is not accompanied by a corresponding assurance of favorable termination of the disease.

The index of resistance was calculated according to Walker's formula. Table II portrays the result. Among the patients who recovered, 32 per cent had indexes which were positive or zero, the rest being minus quantities. The lowest index was −20, shared by 3 patients, all of whom convalesced without incident. The highest index of resistance was +29. This patient also had the highest leukocytosis in the series (55,100). He developed empyema and recovered after thoracotomy. Incidently, his Wassermann reaction was strongly positive.

Among the fatal cases, only 15 per cent had indexes which were positive or zero, the rest being negative. The lowest index in the

group was −31. This patient had a leukocyte count of 5200, with 96 per cent of polymorphonuclears. He died on the ninth day of the disease. All of the 10 patients whose initial index of resistance was below −20 are counted among the fatal group.

TABLE II.—ANALYSIS OF INDEXES OF RESISTANCE OF 100 NON-FATAL AND 60 FATAL CASES OF LOBAR PNEUMONIA.

Index of resistance.	Recovered.		Died.		Total cases.	Recovered, per cent.
	Number.	Per cent.	Number.	Per cent.		
Over +20	1	1	0	0	1	100.0
+11 to +20	6	6	1	2	7	85.7
0 to +10	25	25	8	13	33	75.7
−10 to −1	49	49	20	33	69	71.0
−20 to −11	19	19	21	35	40	47.5
Below −20	0	0	10	17	10	0.0
Total	100	100	60	100	160	

The average index of resistance for the patients who recovered was −3.7; for those who died, −10.5.

Discussion. Up to the present time, the prognostic significance of the differential leukocyte count has been carefully investigated in only a few diseases. Since the question of surgical interference clamors urgently for solution whenever the diagnosis of appendicitis is made, this disease has attracted more attention than any other in this connection. Gibson's general findings have been corroborated by a series of investigators.[8] Other writers have usually chosen a mixed group of acute infectious diseases for their material. It is obvious that conclusions based on the results in a series of cases of acute appendicitis would not necessarily hold for diseases known to call forth peculiar blood responses on the part of the body. The leukopenia-producing diseases, for example, such as influenza and typhoid would require separate study. Since these particular leukopenias are characterized by suppression of polymorphonuclear leukocytes they would doubtless yield uniformly high indexes of resistance not justified by the 10 per cent mortality of typhoid fever. The high lymphocytic percentage in whooping cough and the peculiar blood picture of infectious mononucleosis could be cited as extreme examples of specific types of response of the organism to infections, nullifying attempts to apply prognostic data obtained from one disease indiscriminately to another.

On the other hand, there is a large group of acute infectious processes which usually call forth a polymorphonuclear leukocytosis apparently not of specific type. One might cite the pneumonias, scarlet fever, septicemia and puerperal sepsis, cerebrospinal fever, erysipelas, and the acute pyogenic infections such as appendicitis, peritonitis, mastoiditis, acute lymphadenitis, septic thrombophlebitis, etc. In these, the index of resistance might be expected to yield reasonably consistent prognostic data. It must not be forgotten,

however, that unexplained paradoxical variations are observed from time to time, justifying Wilson's[9] remark that "No sweeping conclusions would be warranted from the . . . data." The present series of cases well illustrates this point.

The small group of patients, constituting 9 or 15 per cent of the fatal cases, who died in spite of indexes of resistance indicating a good outlook (positive or zero) are of especial interest. One can readily conceive of a patient with good resistance immunologically speaking who might nevertheless become exhausted from anoxemia due to wide-spread consolidation of the lungs. None of our cases decisively illustrates this possibility, however. Six of these 9 patients had their counts performed within forty-eight hours of death. Several writers[10] have noted that moribund patients and children constitute two classes whose indexes of resistance are apt to be misleading. Walker made repeated determinations on 46 patients with pneumonia and noted that "in 6 out of 17 deaths, there was observed a sharp and marked antemortem rise to positive. This occurred usually from twenty-four to forty-eight hours prior to death." The exact reason for the death of our other 3 patients in spite of favorable early indexes is less apparent.

It is noteworthy that 68 per cent of the patients who recovered had negative indexes of resistance according to Walker's formula. Seemingly, to judge from our material, the formula is set at too low a pitch and might be altered to advantage in the direction of optimism. We therefore question the wisdom of Walker's alteration of Gibson's normal upper polymorphonuclear leukocyte level from 75 per cent to 70 per cent. Applying Walker's formula with the substitution of Gibson's figure raises any given index of resistance 5 points. In our series this would give an average index of resistance of +1.3 for those who recovered and −5.5 for the fatal cases. The use of such an altered formula would yield 56 per cent of favorable indexes (zero or plus) among the group who recovered and 72 per cent unfavorable (minus) among those who died. Such a readjustment seems to approach somewhat more nearly the balance Walker was aiming at when he originated the term and concept "index of resistance."

In suggesting this change we are aware that the normal differential leukocyte count rarely reveals 75 per cent of polymorphonuclear leukocytes and that Walker is therefore theoretically right. Apparently, however, in the presence of infection with good resistance the percentage of polymorphonuclears frequently rises somewhat more than one unit for every thousand increase in the total count above 10,000. The use of Gibson's higher figure of 75 per cent affords a convenient method of making approximate allowance for this.

Unfortunately, we are not able to claim extreme accuracy for the counts on which this study is based. They were made as a routine

duty by interns who had no idea their work was to be used for an analysis of a series of differential counts. Probably in few cases were more than 100 cells counted. Nevertheless, they are representative of differential counts as routinely done in hospital practice, and it is from such counts that deductions will usually have to be made by the attending physician or surgeon.

Conclusions. 1. Absence of leukocytosis is an unfavorable and leukopenia an ominous sign in lobar pneumonia. A high total leukocyte count, especially 20,000 per c.mm. or above, is reassuring.

2. Suppression of the total lymphocyte count below the low normal of 1200 per c.mm. is of bad import, having been noted in over half of the fatal cases.

3. Among 100 patients who recovered from pneumonia, 68 per cent had negative indexes of resistance at the initial blood count. A negative index of resistance cannot therefore be regarded *per se* as alarming. Nevertheless, a very low index of resistance is unfavorable

4. A slight alteration of Walker's formula is suggested with the object of making it express more nearly the idea for which he designed it.

5. The specific nature of the body's response to various types of infection makes caution necessary in drawing prognostic conclusions from differential counts.

6. The initial total leukocyte and differential leukocyte counts are frequently useful in the prognosis of pneumonia. Paradoxical results are sufficiently common, however, to discourage undue dependence on their prognostic significance.

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ANEURYSM OF THE CORONARY ARTERIES.

Report of a Case.

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The occurrence of aneurysm in the coronary arteries is exceedingly rare. Packard and Wechsler[1] have recently collected 29 cases from the literature, and have added 1 case of their own. Their study showed that the condition was two and a half times as frequent in men as in women. The age of the individuals in which these aneurysms occurred varied between five and seventy-seven, and averaged thirty-seven years. The aneurysms were usually single, and were situated most frequently in the left coronary artery within the first 3 cm. of its course. Rupture of the aneurysm was reported in 12 of the 29 cases in which this phenomenon was mentioned.

The symptomatology of this disease is not typical. Two major types have been observed. In the first of these the patients present a history referable to rheumatic heart disease, usually with a bacterial endocarditis superimposed upon damage due to previous rheumatic infection. In the second type there is the syndrome of angina pectoris or of myocardial degeneration as a result of disease of the coronary arteries. Physical examination reveals nothing that is characteristic. The mode of death is variable. The antemortem diagnosis of coronary aneurysm is, obviously, not possible.

Many of these aneurysms (about 35 per cent) are not classifiable etiologically, due to the varied picture which they present. The apparent etiologic factor most frequently observed (42 per cent) is arteriosclerosis. A second major group (23 per cent) consists of the mycotic-embolic aneurysms, which occur in association with an acute or subacute bacterial endocarditis of the aortic valve. Judging from the associated incidence of syphilitic mesaortitis, which occurred in only 3 of the 31 cases, syphilis is not an important factor in the etiology of aneurysms in this location. The rôle of trauma in the production of coronary aneurysms is not significant.

Packard and Wechsler considered 12 of their series of cases to be unquestionably arteriosclerotic in origin. The case reported here is believed to belong also in this classification. Eleven of these 13

were men, and 2 were women. The age of these individuals varied between thirty-two and seventy-seven, and averaged fifty-six years. In only 3 of the cases, including the 1 here presented, was the aneurysm situated in the right coronary artery. The size of the aneurysms varied between that of a "pea," and 6 cm. in diameter. Rupture of the aneurysm occurred in 5 cases, and was not mentioned in one of the reports. There was a variable mode of death. Seven, including those 5 in which rupture occurred, died suddenly. Three died with symptoms and signs referable to gradual cardiac failure. One died of intercurrent infection, while the manner in which the remaining 2 died was not noted.

Case Report.—A. B. E., a native-born white man, aged sixty-five years, a broker, was seen by one of us (C. D. C.) on May 31, 1929, with complaints of shortness of breath and of generalized swelling. He had always felt well until a few months before the date mentioned. He had known, however, that he had had an elevated blood pressure (180 to 200 systolic) for many years. In January, 1929, he had had a "stroke," involving the entire left side of the body, from which he had recovered sufficiently to be able to move about the house with the aid of a crutch and a cane. He had lost about 20 kg. during the preceding year.

Physical examination revealed a well-developed, somewhat undernourished male. The left side was paretic. There was marked respiratory distress, with periodicity of the Cheyne-Stokes type. The lungs were clear. There was a slight degree of cardiac enlargement, and a systolic murmur was audible at the apex and over the aortic area. The heart was otherwise normal. The palpable arteries were tortuous and sclerotic, but the ocular fundi showed no abnormalities. The pulse rate was 100; the blood pressure 150 systolic, 80 diastolic. The abdomen was normal. There was a considerable degree of edema, involving chiefly the lower extremities.

The urine contained a trace of albumin. The blood urea was 33 mg.

The patient was put to bed, digitalized, and given metaphyllin by mouth. His respiratory mechanism became normal. The edema gradually disappeared. He then weighed about 75 kg. After ten days of bed rest, he was allowed to be up. His blood pressure was still 150 systolic, 80 diastolic, with a pulse rate of 75.

Two weeks later, the patient complained of moderate abdominal discomfort. Physical examination was essentially as it had been, although the abdomen was somewhat distended. Later that day the patient relapsed into a condition of shock, with a pulse rate of 130 and a blood pressure of 80 systolic, 50 diastolic. There was extreme Cheyne-Stokes periodicity, with apneic periods lasting sometimes as long as one minute and nine seconds. The abdomen was markedly distended. On the following evening abdominal distention had disappeared, and a pulsatile tumor, about 10 cm. in diameter, was felt about the point of bifurcation of the abdominal aorta.

Contrary to expectation, the patient gradually improved, and was again able to be up about the house. The blood pressure, however, never resumed its former level, the systolic pressure varying between 70 and 95. About two months later, edema of the extremities reappeared, and respiratory periodicity was again troublesome. From then on the patient's course was constantly downward. There was gradual enlargement of the heart sufficient to place the left border of cardiac dullness outside of the anterior axillary line. There was increasing mental confusion, and the patient was difficult to control. During the last three weeks it was impossible to give him anything by mouth. His edema then became less, the urinary output

was markedly reduced, and he lost weight rapidly. He was moribund for several days, and died October 21, 1929.

*Autopsy Report.** The body, weighing approximately 52 kg. and about 175 cm. long, was that of an emaciated white male appearing to be about sixty-five years of age. There were several decubital ulcers over the sacrum, buttocks and heels. There was nothing else of interest on external examination except an asymmetry of the lower abdomen produced by an intra-abdominal tumor mass which caused a firm nodular elevation, about 6 cm. in circumference, below and to the right of the umbilicus.

The examination was limited to an abdominal incision. On section, no abnormalities of the subcutaneous tissues or of the serous cavities were observed.

The heart weighed 500 gm. Hypertrophy and dilatation were generalized, but particularly marked on the left side. The myocardium at the apex, and extending upward anteriorly, laterally and posteriorly for several centimeters, had been replaced by dense fibrous connective tissue. The wall at the apex itself was not more than 3 mm. thick. The endocardium over this extensive area of myocardial cicatrization was opaque and fibrous. The right ventricular wall measured about 5 mm. in thickness. The septum was thin and the septal endocardium was thick and fibrous. The papillary muscles and the columnæ carneæ were atrophic and flattened. No intraventricular thrombosis was present. The valves and valve orifices showed only a moderate degree of sclerosis.

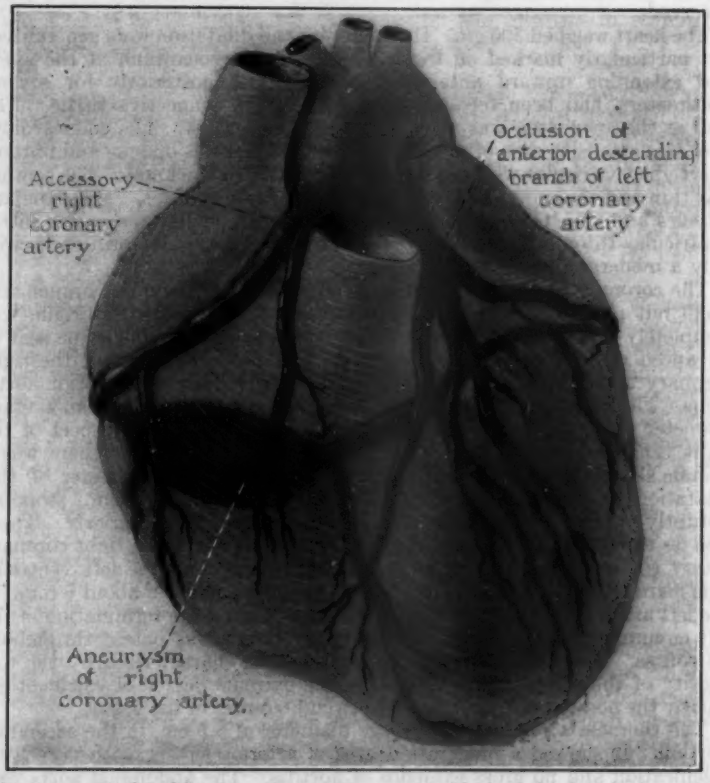
The coronary orifices were not unusual. The left circumflex branch was small but patent. The left ramus descendens, just below its origin, was completely occluded by old organized thrombosis in a segment the seat of advanced arteriosclerosis and calcification. The first branch of the right coronary artery had an anomalous origin direct from the anterior aortic sinus. The main trunk of the vessel was unusually large, having an average diameter of about 7 mm. until it had reached the posterior aspect of the right ventricle, where, in the medial atrioventricular groove, there was a spindle shaped dilatation. (See illus.) The maximum diameter of this dilatation was 2.5 cm. and it extended a distance of 4.5 cm., stopping abruptly at the junction of the interventricular septum posteriorly. There was no thrombosis in this aneurysm. Large branches of the right coronary artery coursed obliquely across the posterior aspect of the left ventricle. The main trunk of the vessel continued, with a diameter of about 6 mm., in the left atrioventricular sulcus, and extended beyond the termination of the left circumflex branch. The right coronary artery was patent throughout its course. The entire coronary circulation was characterized by the tortuosity of the secondary branches, by the extreme degree of calcification, and by the nodular inequalities in the circumferences of the vessels.

The thoracic aorta had an average diameter of 8.5 cm. in the ascending portion. It showed a moderate degree of arteriosclerosis, with very little calcification and no gross evidence of aortitis. The abdominal aorta presented a picture of marked and extensive atherosclerosis, with calcification, ulceration and intimal thrombosis. There were a number of small pouch-like dilatations of the wall. Immediately below the origin of the inferior mesenteric artery, and extending from there to the bifurcation, there was a saccular dilatation of the aorta, measuring 11 cm. in diameter. This dilatation was eccentric, lying mostly to the right. The sac was almost entirely filled with lamellar thrombus, and this thrombosis extended somewhat above and below.

The branches of the abdominal aorta showed a similar degree of sclerosis and nodular inequalities in their circumferences. The celiac axis had a

* We are indebted to Dr. Alan R. Moritz, the pathologist of the Lakeside Hospital, for the privilege of reporting these findings.

diameter of 1 cm. at its origin, 14 mm. at its first division, and its gastrohepatic branch terminated in three hepatic branches with average diameters of 5 mm. The superior mesenteric artery reached, in places, a diameter of 13 mm.; in other places it did not exceed 1 cm. The inferior mesenteric and the renal arteries revealed similar changes. The common iliac arteries arose directly from the inferior pole of the aortic aneurysm. The left had a fairly uniform diameter of about 2 cm., but the right varied between 1.5 cm. at its origin and 3.5 cm. a little farther along. Both of these arteries were the seat of thrombosis, the clot being continuous with that in the aneurysmal sac.


Occlusion of anterior descending branch of left coronary artery
Accessory right coronary artery
Aneurysm of right coronary artery

Aneurysm of the right coronary artery, presumably arteriosclerotic in origin. There was severe generalized arteriosclerosis. The ramus descendens of the left coronary artery was obliterated by organized thrombosis, with resulting myocardial infarction.

The inferior vena cava was firmly adherent to the surface of the aortic aneurysm. It was collapsed and stretched to such an extent that its intimal surfaces were closely approximated, but there was no thrombosis. The left renal vein was completely obliterated by organized clot.

The liver weighed 900 gm. Except for atrophy and for the unusually small hepatic arteries, there was no pathologic change.

The kidneys weighed, together, 200 gm. Their contour was grossly

irregular, and in addition to both coarse and fine granularity of their surfaces, there was evidence of multiple old and recent infarction. The cortex was reduced and variable in width.

Histologic sections of the heart, cut so as to include branches of the coronary arteries, showed marked intimal thickening of the vessels, with extensive hyaline degeneration and calcification. In some instances the degeneration was limited to the intima but in other areas the entire wall of the vessel appeared to be involved. Little or no inflammatory reaction was noted in connection with this sclerosis. The sclerotic changes were relatively less severe in the smaller branches. The lumina of the arteries were reduced in size to a varying degree, even to obliteration. The myocardium was characterized by large areas of cicatrization, some of which were recent and showed fibroblastic proliferation and vascularization, while others were older and showed complete replacement of muscle by dense hyalinized scar tissue.

Sections from the aorta showed great thickening of the intima, with hyaline and fatty degeneration, and areas of necrosis filled with structureless granular material. Acicular spaces in this necrotic material suggested the sites of crystalline deposition. The surface of the intima was roughened, and attached to these roughened surfaces were thrombus masses. The media showed extensive calcification and hyaline and myxomatous degeneration, which in some places closely approached the adventitia. In one large plaque of medial calcification true bone formation was observed. Throughout the aorta and the medium-sized arteries there was extensive interruption of continuity of the elastica. The adventitia showed considerable focal lymphocytic infiltration, with some tendency to perivascular distribution, but the vasa vasorum did not show obliteration. Where the focal degeneration of the media bordered on the adventitia there was, in some instances, organization, as manifested by loose granulation tissue extending from the adventitia into the necrotic areas.

The pathologic diagnosis was: aneurysm of the right coronary artery; aneurysm of the abdominal aorta; aneurysm of the right common iliac artery; generalized arteriosclerosis, severe; thrombosis and obliteration of the ramus descendens of the left coronary artery; atheromatous ulceration and intimal thrombosis of the aorta; thrombosis of the common iliac arteries; thrombosis of the left renal vein; infarction of the myocardium; infarction of the kidneys; cardiac hypertrophy and dilatation; arterial and arteriolar nephrosclerosis; anomaly of the right aortic sinus; atrophy of the liver; decubital ulcers; emaciation.

The pathologic changes in the arteries were essentially degenerative, and were most pronounced in the media. There was accompanying degeneration and productive inflammation of the intima. This inflammation appeared to be secondary to the degeneration. Fragmentation of the elastica was prominent, and seemed to be spontaneous rather than the result of inflammatory destruction. This deterioration of the elastica presumably permitted a generalized dilatation of the larger bloodvessels, which in three instances was of aneurysmal size.

Summary. 1. A case of aneurysm of the right coronary artery is reported.

2. There were no clinical findings suggesting this lesion.

3. In addition to the coronary aneurysm, and to nodular inequalities in the circumferences of the medium-sized arteries, there was a large saccular aneurysm of the abdominal aorta, and a fusiform aneurysm of the right common iliac artery. There was an extreme

degree of sclerosis of the coronary arteries, with occlusion of the left ramus descendens and extensive myocardial infarction.

4. This is the thirty-first instance which we have found in the literature of aneurysm of the coronary arteries.

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THE SIGNIFICANCE OF SINUS ARRHYTHMIA IN OLD PEOPLE.

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It is the purpose of this paper to call attention to a type of sinus arrhythmia occurring in old people which, in contradistinction to the type seen in youth, appears to have some pathologic significance.

Sinus arrhythmia is an irregularity in the cardiac rhythm resulting from changing rates of discharge of impulses in the sinoauricular node. The cardiac rate at any given moment is the resultant of two forces acting on this node—the vagus and the sympathetic. In young people it is periodic alterations in vagal tone associated with the phases of respiration which produce the alternate acceleration and deceleration of the heart rate, known as sinus arrhythmia. Einthoven[1] clearly demonstrated the reflex nature of this phenomenon in 1908. He showed that sinus arrhythmia was abolished by atropin or by vagal section, and he recorded by means of the string galvanometer rhythmic action currents passing up the vagus nerve in the dog (Chart 1). These action currents have a double rhythm, consisting of large, slow oscillations corresponding with the respiratory rate, and small, rapid oscillations corresponding with the heart rate. In rabbits, where the depressor nerve is separate from the vagus, he demonstrated that the vagus nerve shows exclusively respiratory oscillations while the depressor nerve shows only heart beat oscillations. Stimulation of the central end of either vagus or depressor nerve causes slowing of the heart. Of these two reflex mechanisms in the healthy heart it is apparently only the afferent impulses from the respiratory system which reach a magnitude sufficient to alter the cardiac rhythm.

As to the clinical significance of this irregularity, it has been generally regarded to have no pathologic significance and, indeed,

to be a favorable prognostic sign if found in the presence of heart disease.[2] Sir James Mackenzie[3] stated that he has "Never seen the presence of this irregularity in an acute infection or with a progressive lesion of the heart muscle."

However, Wedd,[4] in 1921, stated that sinus arrhythmia may not only exist in the presence of organic heart disease but may actually be a manifestation of it. He appears to have been the first to point out the possible rôle of afferent impulses from a diseased heart or aorta in producing sinus arrhythmia. Wedd says: "Just as in certain pathologic states impulses may arise in the heart which give rise to sensations of pain, so it is believed that in other abnormal conditions impulses may form in the heart or aorta, which, transmitted by the afferent fibers of the vagus of the cardiac depression nerve to the inhibitory center, will become manifest as disturbances of the cardiac mechanism."

There follows a summary of 4 cases of sinus arrhythmia in the presence of arteriosclerotic heart disease which have come under my observation.

Case Reports. CASE I.—A male, aged eighty-seven years (Johns Hopkins Hosp. Ecg. No. 6271), was moribund and died within twenty-four hours of his entrance to the hospital. A satisfactory history was not obtained. Physical examination showed general anasarca to be present. The heart was enlarged to the left by percussion. Its sounds were weak and totally irregular. The blood pressure was 88/60. The urine contained a trace of albumin. The nonprotein nitrogen in the blood was 32 mg. per 100 cc. Phthalein test 14 per cent excreted in two hours. An electrocardiogram showed marked sinus arrhythmia; partial heart block; *P–R* interval 0.23 seconds; *Q–S* interval 0.08 seconds; some slurring of *Q–R–S* in all leads. *T* wave inverted in all leads.

A diagnosis was made of arteriosclerotic heart disease, myocardial insufficiency and carcinoma of the prostate.

CASE II.—A male, aged seventy years (Boston City Hosp. No. 571253), entered the hospital complaining of productive cough of several days' duration. He had suffered from increasing dyspnea for about five years.

Physical examination showed marked peripheral arteriosclerosis, a barrel-shaped chest, and musical and crepitant râles at the bases of the lungs. The heart appeared to be enlarged slightly and presented a curious irregularity consisting of runs of 10 or 12 rapid beats alternating with 10 or 12 slow beats. The blood pressure was 120/60. There was no peripheral edema. An electrocardiogram on day of admission showed marked sinus arrhythmia, rate 80 to 90, *P–R* interval 0.14 seconds, *Q–S* interval 0.08 seconds. *T*-wave upright in all leads. Two days later the arrhythmia was less marked and nine days later it had disappeared altogether. The patient improved on rest in bed and was discharged after one month with a diagnosis of acute bronchitis, arteriosclerosis, chronic myocarditis, sinus arrhythmia. Both bronchopneumonia and pulmonary tuberculosis were considered to be perhaps present in addition.

CASE III.—A male, aged sixty-one years (Boston City Hosp. No. 577915), entered the hospital complaining of chill and productive cough. He gave a history of a number of attacks of severe precordial pain associated with

dyspnea which were not brought on by exertion. He had no dyspnea on exertion.

Physical examination showed well-marked peripheral arteriosclerosis and emphysema. There were many crepitant and musical râles throughout both lungs. There was no peripheral edema. A Roentgen ray examination of the chest showed enlargement of the heart to the left but a "seven-foot plate" was not taken. Electrocardiograms showed marked sinus arrhythmia, rate 50 to 60, *P–R* interval 0.16 seconds, *Q–S* interval 0.12 seconds; *T* wave diphasic in Lead I, upright in Lead II, and low in Lead III. The *Q–R–S* complexes were slurred in all leads. The electrocardiographic diagnosis was: sinus arrhythmia, intraventricular block with perhaps right bundle branch block.

By means of synchronous pneumographic and electrocardiographic records it was possible to demonstrate graphically in this case what had been suspected to occur in the two previous cases, namely, that the cardiac rhythm bore no relation to the phases of respiration. Indeed, there were at times long periods of bigeminal rhythm due to sinus arrhythmia. Inhalation of amyl nitrate sufficient to lower the blood pressure from 110/70 to 90/60 and to raise the pulse rate from 60 per minute to 80, caused no decrease of the arrhythmia. Vagal pressure produced marked slowing of the heart rate with ventricular escape. After administration of atropin sulphate, 1/60 gr. (0.001 gm.) intravenously, the heart rhythm became regular at a rate of 72 and vagal pressure no longer produced slowing.

This patient's arrhythmia persisted during the six weeks he stayed in the hospital.

He was considered to have bronchopneumonia, bronchial asthma, arteriosclerotic heart disease, coronary sclerosis, and generalized arteriosclerosis.

Case IV.—A male, aged seventy-five years (Boston City Hosp. No. 579673), complained of shortness of breath and precordial pain on exertion. He had rheumatic fever at the age of eighteen years but did not experience any symptoms of cardiac disease, until five years ago, when he began to have substernal pain on exertion with moderate degree of dyspnea and edema of the ankles. This man was treated in a hospital for cardiac decompensation at that time, when the cardiac rhythm was noted to be regular. In the course of five hospital admissions the physical signs in the heart underwent an interesting evolution. On the first admission only a high-pitched systolic murmur maximal in the aortic area and transmitted over the entire precordium was heard. On the third admission a thrill was felt over the aortic area and a faint early diastolic murmur at the apex of the heart. On the fourth admission the rhythm was irregular, and on the fifth and last admission the above signs were all present in addition to diastolic murmurs in both the aortic and mitral areas. The patient had also extensive peripheral arteriosclerosis, cyanosis, and moist râles at the bases of both lungs. The heart was markedly enlarged to the left, as shown by a "seven-foot Roentgen ray plate" (transverse diameter of heart 19.2 cm., internal diameter of thorax 28 cm.). An electrocardiogram showed sinus arrhythmia with a heart rate approximately 65, partial heart block *P–R* interval 0.28 seconds, intraventricular block, *Q–S* interval 0.11 seconds. Slurring or notching of *Q–R–S* complex occurred in all leads. The *T* wave was inverted in Lead I, upright in Leads II and III. Synchronous pneumographic and electrocardiographic records showed that there was generally an acceleration of the cardiac rate with inspiration and slowing with expiration. Admission of 1/40 gr. (0.0015 gm.) of atropin sulphate intravenously raised the cardiac rate from 48 to 60 beats per minute, and lessened, but did not abolish, the arrhythmia. It did not alter the *A–V* conduction. This patient had no attacks of angina pectoris while in the hospital. The

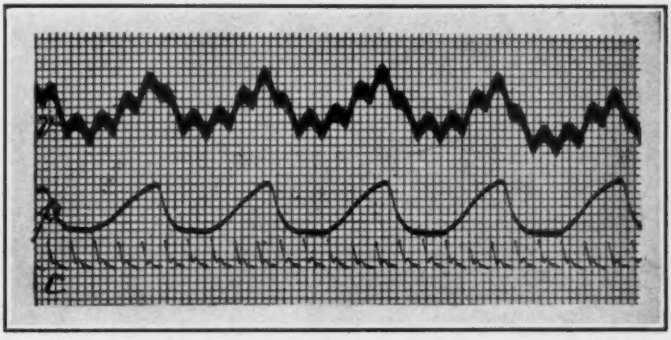

CHART 1.—Figure showing the electrical changes in the vagus nerve which accompany the respiratory and heart movements. *v*, Electrovagogram; *p*, respiration record (ascent of curve, inspiration; descent, expiration); *c*, pulse record. (After Einthoven.)

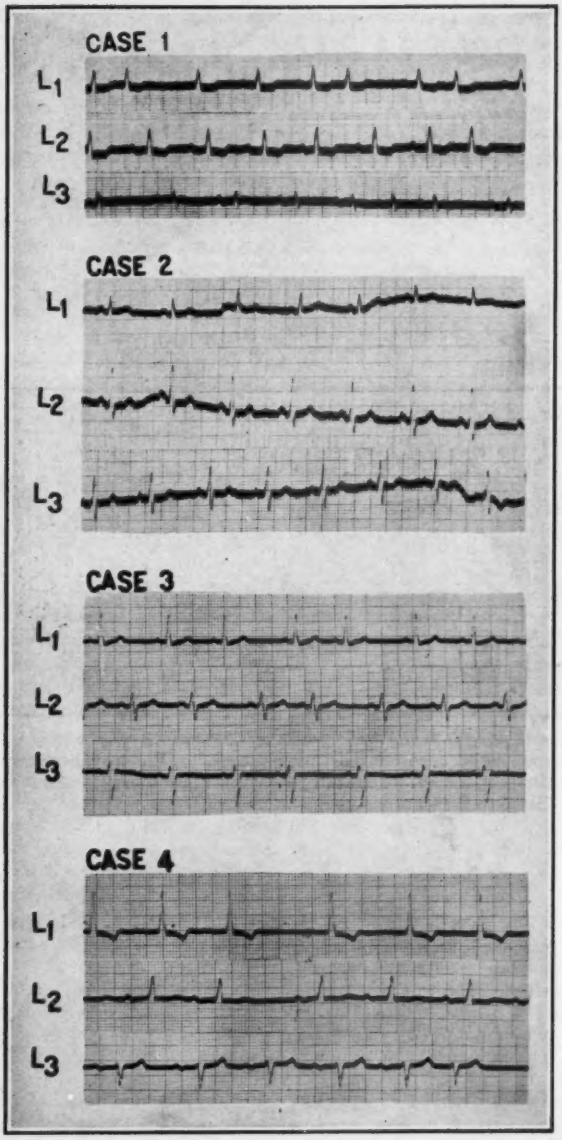

CHART 2.—Electrocardiograms of 4 cases of sinus arrhythmia in old people. See text. Customary lead and standardization.

arrhythmia persisted but the dyspnea gradually subsided; the râles disappeared from his lungs; and after six weeks he was discharged from the hospital with the diagnosis of aortic stenosis and regurgitation, mitral stenosis and regurgitation, cardiac decompensation, generalized arteriosclerosis, rheumatic heart disease (?), arteriosclerotic heart disease (?), asthmatic bronchitis, emphysema, partial heart block, and sinus arrhythmia.

Discussion. The observation of this "benign, youthful irregularity," as Mackenzie termed it, in older people with advanced organic heart disease, led me to examine hospital records in order to determine its incidence and, if possible, its clinical significance. For this purpose I have analyzed all the cases with an electrocardiographic diagnosis of sinus arrhythmia at the Johns Hopkins Hospital, and all such cases over fifty years of age at the Boston City Hospital.

At the onset all cases showing auricular extrasystoles were excluded because it was believed that sinus arrhythmia in association with these ectopic contractions is a secondary phenomenon brought about by extrasystolic beats. It was also recognized that sinus arrhythmia is not infrequently seen for varying periods following reversion to sinus rhythm after auricular fibrillation, auricular flutter or paroxysmal auricular tachycardia, whether the reversion be induced by drugs, such as quinidin or digitalis, or whether it be spontaneous. Under these circumstances sinus arrhythmia does not perhaps have the same significance as when it is not preceded by an abnormal rhythm. It has been impossible to exclude such cases from this series, however, because a large percentage of elderly patients with sinus arrhythmia come to the cardiographic laboratory with a mistaken clinical diagnosis of auricular fibrillation.

Digitalis in large doses is said at times to cause disturbance of the sinus rhythm, but it does not appear to be an important factor in this series because in only 1 case of sinus arrhythmia was there recorded clinical evidence of digitalis poisoning.

In the electrocardiographic records of the Johns Hopkins Hospital up to August, 1927, there were 138 cases of sinus arrhythmia, amounting to 4 per cent of the total electrocardiograms taken. These records show a decreasing incidence of sinus arrhythmia with advancing years. In patients under thirty-five years the incidence is about 12 per cent. Above the age of thirty-five years the incidence drops down to about 5 per cent and above the age of fifty years sinus arrhythmia is rare, occurring in only 23 cases or 1 per cent of the total cases above that age.

In the group of patients under fifty years of age the most common clinical diagnosis was hyperthyroidism. This diagnosis was established for 18 cases (17 per cent). Rheumatic heart disease was the next most frequent diagnosis, with 8 cases (8 per cent). Luetic heart disease was present in 5 cases (5 per cent). In the patients over fifty years of age naturally arteriosclerotic heart disease was the most common diagnosis, occurring in 33 per cent of the cases.

Hypertensive heart disease and luetic heart disease formed 16 per cent of the cases in the older patients. Myxedema was the diagnosis for 1 case.

A more striking contrast between the two groups is obtained if one considers the number of cases in each group that showed presumptive evidence of organic cardiac disease on physical examination, or by electrocardiographic examination. The criteria used were, briefly, the presence of undoubted signs of congestive heart failure, diastolic murmurs, pulsus alternans, cardiac enlargement or aortic dilatation as determined by Roentgen ray examination or by electrocardiographic demonstration of *A–V* block, intraventricular block, or inversion of the *T* wave in Lead II in the absence of digitalis therapy. Twenty-four per cent of the younger patients showed presumptive evidence of organic cardiac disease, and only 10 per cent had congestive failure. This is in contrast to the patients over fifty years of age, of whom 65 per cent had evidence of organic heart disease and 33 per cent had congestive failure.

At the Boston City Hospital satisfactory records were available for 22 patients with sinus arrhythmia over fifty years of age. Sixteen of the patients had arteriosclerotic heart disease, 4 had luetic heart disease and 2 had rheumatic heart disease. Four of these individuals suffered from angina pectoris. The last patient to be accounted for had myxedema. In this case the sinus arrhythmia disappeared under thyroid extract therapy coincident with which there was a return of the low electrocardiographic complexes to normal height.

For comparison the records of 100 ward patients over fifty years of age who showed sinus rhythm by electrocardiogram were picked at random from the files and studied. It was found that 23 patients, or 85 per cent of those with sinus arrhythmia showed presumptive evidence of organic heart disease, as compared to 57 per cent of the 100 patients with normal cardiac rhythm. The percentage of cases with signs of congestive failure was slightly higher in the sinus arrhythmia group, totaling 14 cases, or 50 per cent as compared to 46 per cent of the normal rhythm group.

The above figures appear to indicate that sinus arrhythmia is not always a benign irregularity, for, in older people, it is more apt to be associated with organic heart disease than is normal rhythm. This type of sinus arrhythmia found in old people, in marked contrast to the youthful type of sinus irregularity, is often met with in the presence of advanced and progressive heart disease. An additional distinguishing feature is that the sinus irregularity of old age frequently bears no relation to the phases of respiration. These findings suggest the probability that there are two distinct types of sinus arrhythmia, having a different mode of origin—a youthful type which is directly related to normal phasic variations in vagal tone corresponding to the phases of respiration, and a type

seen in older people which may bear no relation to the respiratory rhythm and which, indeed, may be a response to abnormal afferent impulses arising in a diseased heart or aorta.

Summary. 1. The pathologic significance of 4 cases of sinus arrhythmia in old people with organic heart disease is discussed.

2. Analysis of hospital records shows that sinus arrhythmia in patients over fifty years of age is more frequently associated with evidence of organic heart disease than is normal rhythm.

3. Support is lent to the suggestion of Wedd that sinus arrhythmia may at times represent a reflex response to abnormal efferent stimuli from a diseased heart or aorta.

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THE SYMPTOMATOLOGY OF ARTERIAL HYPERTENSION.

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The Complaints of Patients With Uncomplicated Hypertension. The greater part of our knowledge of essential hypertension dates back less than twenty years. During this short period a close connection has been demonstrated between persistently elevated blood pressure and pathologic changes in the kidney, heart, brain and bloodvessels. The existence of hypertension can easily be determined with the sphygmomanometer, but it is frequently difficult to prove the presence of complications, especially in their incipient stage. This often can be done, however, by a critical analysis of all the information derived from the patient's clinical history, from a careful physical examination, and from the laboratory tests performed on the blood and urine.

Perhaps because of the ease with which the diagnosis of hypertension can be made and possibly because the condition has been studied intensively for less than two decades, relatively little attention has been paid to the symptomatology which accompanies high

blood pressure. There are few reports which state the frequency with which symptoms have been found (Table I). Even these

TABLE I.—SYMPTOMATOLOGY OF HYPERTENSION.

Kauffmann[1] 48 cases.		Schultz and Biehn[2] 114 cases.		Paullin, Bowcock, Wood[3] 500 cases.		Douthwaite[4] 43 cases.	
Symptom.	Per cent of cases.	Symptom.	Per cent of cases.	Symptom.	Per cent of cases.	Symptom.	Per cent of cases.
"Rheumatism"	68.4	Restlessness	29.8	Nocturia	49.0	Dyspnea	55.4
Dizziness	58.2	Insomnia	28.0	Cerebral crises	11.2	Palpitation	51.2
Hypersensitivity to warmth	47.9	Palpitation	22.8	Dyspnea	11.0	Headache	44.2
"Migraine"	43.8	Generalized fatigue	16.7	Angina pectoris	8.4	Giddiness	23.3
Morning headache	33.3	Constipation	16.7	Substernal oppression	5.6	Tinnitus	20.7
Angiospasm	12.5	Depression	16.7	Vertigo	3.6	Hemorrhage	13.9
		Dyspnea	14.0	Tinnitus	3.4	Sense of choking	9.3
		Irritability	14.0	Hemorrhage:		Angina	4.6
		Pressure on the head	13.2	Nasal	3.0	Miscellaneous	
		No desire to work	13.2	Conjunctival	1.2	Indigestion	
		Fatigue of arms	11.4	Uterine	0.8	Fleeting pains	
		Rheumatic complaints	10.5	Pulmonary	0.2	Loss of memory	
		Fatigue of legs	10.5	Intestinal	0.2	Nervousness	
		Anxiety	9.6	Intermittent claudication	0.6	Insomnia	
		Dizziness	8.8			Nocturia	
		Migraine	7.9				
		Tinnitus	5.3				
		Boring headache	4.4				
		Poor memory	3.5				
		Early generalized fatigue	2.6				
		Loss of appetite	2.6				
		Sleepiness	2.6				
		Sensitivity to poor ventilation	1.7				
		No symptoms	8.8				

reports fail to differentiate between the early and late symptoms of hypertension and to throw light on the general significance of the symptoms observed. There is also a lack of knowledge concerning the relationship between the symptoms referable to hypertension and those observed in other diseases. Kauffmann[1], Schultz and Biehn,[2] Paullin, Bowcock and Wood,[3] and Douthwaite[4] have examined the histories of patients with hypertension and have reported the symptomatology. These four investigations together include about 700 cases; but 500 of these cases, studied by Paullin, Bowcock, and Wood,[3] were studied from the point of view of the complications of hypertension, and therefore the symptoms exhibited by this group of patients may well bear rather on the cerebral, cardiac or renal complications, than on hypertension in itself. We have included in Table I those subjective symptoms which they listed as complications.

The symptomatology which we are to present here is based on an analysis of the records of 1090 uncomplicated cases* selected from the 1628 cases of hypertension discovered among the patients visiting the medical outpatient department of the Boston City Hospital during the forty-two months from January, 1926, to June, 1929, inclusive. So far as hypertension is concerned, outpatient cases are relatively free from the disabling complications of this condition seen in the majority of patients with hypertension who enter hospital wards. This situation is of advantage in determining the symptomatology of arterial hypertension *per se*, for the histories of cases with complications deal in the main with the symptomatology of the complicating pathologic condition. It was, then, to obtain complete records of uncomplicated cases of hypertension that the records of 538 patients were discarded.

The 1090 records then remaining represented cases of uncomplicated hypertension whose case histories were adequate and reliable. These cases were made up of 289 men and 801 women. The systolic pressure was 160 mm. Hg. or above in 90.2 per cent of the instances; the diastolic pressure was 100 mm. Hg. or above in 64.5 per cent of the cases. The blood pressure was observed to be elevated on repeated occasions.

TABLE II.—SYMPTOMATOLOGY OF HYPERTENSION. BASED ON THE RECORDS OF 1090 PATIENTS WITH ELEVATED BLOOD PRESSURE AND NO RELATED DISEASE.

Symptom.	Number of cases.	Per cent of 1090.
Headache	473	43.3
Dizziness	440	40.3
Aches and pains	422	38.7
Dyspnea	302	27.7
Nycturia	283	25.9
Nervousness	144	13.2
Palpitation	143	13.1
Tinnitus	129	11.8
Weakness	126	11.6
Insomnia	61	5.6
Epistaxis	61	5.6
Precordial pain	58	5.3
Numbness and tingling	48	4.4
Edema	46	4.2
Spots before the eyes	44	4.0
Hot flashes	24	2.2
Cramps	17	1.6
Nausea or vomiting	13	1.2
Blurred vision	11	1.0
"Angiospasm"	9	0.8
Throbbing	7	0.6
Hemoptysis	6	0.6
Fainting spells	6	0.6
No symptoms	129	11.8

* The term uncomplicated hypertension is used to define persistently elevated arterial blood pressure of the greater circuit without clinical evidence of impaired cerebral, cardiac or kidney function.

The symptoms which occurred in these cases are presented in Table II in the order of the frequency with which they were recorded. It is obvious that an analysis of records obtained by different individuals does not give such detailed and exact information as that of records taken by the same individuals especially interested and experienced in the disease. Doubtless the percentage frequency of many of these symptoms would be higher in a series of cases which could be followed over a long period of time or in cases where the existence of each of these symptoms was specifically searched for in each patient.

Headaches occurred in 43.3 per cent of the cases. The location varied but the headache was constant for each individual. The discomfort occurred at any time of the day but was most frequently noted in the early morning or evening. The character varied from sharp to dull pain, but it was usually steady; less frequently did a patient complain of a throbbing headache.

Dizziness, a symptom which was almost as frequent (40.3 per cent), occurred in varying degrees of severity but was always very distressing to the patient. Usually it consisted of a sense of giddiness or light headedness but occasionally there was true vertigo. Caloric ear tests when performed were uniformly negative. The dizziness was brought on or accentuated by change of position. This was the outstanding characteristic of the symptom. Although dizziness occurred at any time of the day, it was most frequent immediately after rising in the morning and after retiring at night. Dizziness and headache commonly occurred together or alternately in the same individual. This was the case for 60 per cent of the patients who had headaches and for 64.8 per cent of those with dizziness.

Somatic Aches and Pains were distressing to both patient and examiner, for no adequate cause could be found and no treatment gave more than temporary relief. The pains were of various sorts—sharp, dull, or aching, but usually vague and indescribable. The location and distribution were bizarre: in some cases they were limited to one small region, in other instances they were generalized or migrating from one spot to another, while in still others the sensation was sharply limited to one large area which had no demonstrable neurological distribution. In many of the cases the aches came only on rainy or damp days, while others had the sensation continually and were relieved only when they had something else to distract their attention. Frequently when the pains were referred to the region of a joint it was diagnosed as being due to "chronic arthritis." This was the situation in 21.5 per cent of the cases who complained of aches and pains. Visceral pain was very infrequent.

These vague yet very real complaints appear to have no common bases. Douthwaite[4] has suggested that the pains might be due to a stretching of the bloodvessels as could occur with the patient's increased activity, but in our series of cases no constant relation was

found to exist between the pains and motion. In practically all instances the pains were relieved by physiotherapy but this relief was only temporary.

It will be noted that while headaches (43.3 per cent), dizziness (40.3 per cent), and vague somatic pains (38.7 per cent) occurred in about the same frequency, dyspnea, which was the next most frequent symptom, occurred in but 27.7 per cent of the cases. Not only were [the first three symptoms found with essentially the same frequency, but they often occurred in the same individuals (see Table III).

TABLE III.—NUMBER OF CASES COMPLAINING OF HEADACHES, DIZZINESS AND PAINS, ALONE AND IN COMBINATION WITH EACH OTHER.

Symptom.	Number of cases.
Headaches	473
Dizziness	440
Aches and pains	422
Three above symptoms in one case	117
Headaches and dizziness	168
Headaches and pains	74
Dizziness and pains	53
Headaches alone	114
Dizziness alone	102
Pains alone	168

Dyspnea and nycturia form a second group of complaints which occurred in approximately the same number of cases. There were, however, 97 patients who complained of both symptoms.

Dyspnea on Exertion was recorded in 27.7 per cent of the 1090 cases without complications. In none of these instances did there appear to be enough evidence to justify a diagnosis of myocardial insufficiency. Table IV shows the number of cases in which there occurred combinations of the four symptoms, dyspnea, palpitation, cardiac pain and edema, frequently seen in cardiac failure. Fifty-nine per cent of the patients with dyspnea did not complain of any of these other three symptoms. Only two records showed a history of orthopnea, a symptom which was practically universal in those patients who were diagnosed to be suffering from myocardial damage.

Nycturia occurred in 25.9 per cent of the cases. This symptom may be caused by various conditions and it is often difficult to determine the etiology in any single instance. In some cases it was apparently a habit developed earlier in life, in other instances insomnia was probably the underlying cause. In most cases the etiology was unexplained but in none of these instances were signs of renal damage discovered.

"*Nervousness*" was a term used to denote a variety of closely related symptoms. It included a tendency to worry, to become easily upset, or to become excited over matters of little importance.

Patients with such difficulties were frequently introspective, tending to dwell at undue length on their complaints, or were unstable emotionally. This sort of condition was noted in 13.2 per cent of the cases.

Palpitation of the Heart. The frequency with which this complaint occurred in combination with other cardiac symptoms, has already been referred to (Table IV). There were 20 patients who complained of both palpitation and nervousness.

TABLE IV.—COMBINATIONS OF DYSPNEA, PALPITATION, CARDIAC PAIN AND EDEMA.

Symptom.	Number of cases.
Dyspnea (total)	302
Palpitation (total)	143
Cardiac pain (total)	58
Edema (total)	46
Dyspnea and palpitation	60
Dyspnea and cardiac pain	17
Dyspnea and edema	14
Dyspnea and more than one of the other symptoms	25

Tinnitus was a complaint which was very distressing to the patient. It was present in 11.8 per cent of the cases. It was usually bilateral. The sound was, as a rule, steady and continuous, less when the attention was distracted and more prominent at night or when the patient was quiet and resting. In 74.6 per cent of the cases with tinnitus the patients complained of either headache or dizziness (Table V).

TABLE V.—THE NUMBER OF CASES WITH TINNITUS ASSOCIATED WITH HEADACHES OR DIZZINESS.

Symptom.	Number of cases.
Tinnitus (total)	129
Tinnitus, headache and dizziness	47
Tinnitus and headache	26
Tinnitus and dizziness	23

Weakness. Under this heading is included both increased ease to fatigue and also a subjective sense of weakness or loss of muscular power, the latter usually being referred to the extremities, especially to the legs. These symptoms were seen in 11.6 per cent of the patients with high blood pressure. Schultz and Biehn[2] have determined the frequency with which such symptoms were referred to various parts of the body, but in our series of cases no attempt has been made to classify in detail the areas involved.

The symptoms "nervousness," palpitation of the heart, tinnitus and weakness (Table II) occurred with apparently equal frequency. Other symptoms were recorded in no more than 5.6 per cent of the cases. Nevertheless, several of them deserve special mention.

Epistaxis has received considerable emphasis in the literature. It was noted in but 5.6 per cent of the Boston City Hospital cases. Paullin, Bowcock and Wood[3] found it in 3 per cent of their series, while 39 of the patients reported by Douthwaite[4] complained of hemorrhages from various parts of the body.

Despite the comparative infrequency of epistaxis, it possesses striking characteristics which show that it is an important sign. In 14.8 per cent of the patients who complained of nasal hemorrhage this was the sole complaint. In a great many instances the bleeding took place in the morning as the patient was rising from bed and in many others the epistaxis was brought on by exercise or emotion.

The bleeding rarely yielded to simple measures applied by the patient; cauterization was frequently of no avail, and repeated packings were often resorted to before the flow of blood was stopped. Probably hemorrhage from other parts of the body have the same etiological basis but these were very rare occurrences. Hemoptysis of unknown etiology was seen in 6 cases and there were two instances of unexplained rectal bleeding.

Numbness and Tingling. This type of sensation occurred in 4.4 per cent of the patients, and probably should be classed as a variation of the symptom discussed as "aches and pains." One-third of the cases with numbness and tingling also complained of vague generalized pains. In some cases this symptom was so prominent as to suggest combined system degeneration of the spinal cord, but such a diagnosis was never substantiated.

Edema (4.2 per cent) was never marked. It consisted usually of a slight swelling of the ankles noticeable toward the end of the day. The occurrence of this symptom was usually ascertained only after questioning the patient specifically. *Hot flashes* (2.2 per cent) occurred in 2 men and 22 women. In the women the menopause period had been passed through many years previously. *Cramps* (1.6 per cent) were confined to the legs, especially the calves, and occurred most frequently at night. Under the term *Angiospasm* (0.8 per cent) are included temporary paralyses, aphonias, and the like, which cleared up a few days after their onset and left no residual signs or symptoms. There were 7 patients (0.6 per cent) who complained of a *throbbing* sensation in various parts of the body other than the head.

It is difficult to determine the time of onset of these relatively rare complaints for the majority developed so gradually that a definite history of onset was not obtainable. In Table VI the complaints of the 156 (14.3 per cent) monosymptomatic cases are tabulated, and these probably represent the early symptomatology. It will be seen that pain of some sort was complained of in almost one-half of the cases.

There were 129 patients with hypertension who had no symptoms whatsoever. These cases were discovered among patients who came

to the medical outpatient department for routine physical examination or because of some disorder not related to the circulatory or renal systems. No relationship could be found between the height of the blood pressure and the severity, number or type of complaints. Several patients with blood pressures above 250 mm. Hg. had no symptoms whatsoever. Many patients showed fluctuations in the degree of hypertension without a corresponding variation in the severity of their complaints.

TABLE VI.—COMPLAINTS OF 156 MONOSYMPTOMATIC CASES OF HYPERTENSION.

Symptom.	Number of cases.	Per cent of 156.
Aches and pains	66	42.4
Headache	19	12.2
Dizziness	17	10.9
Nycturia	14	9.0
Dyspnea	9	5.8
Epistaxis	9	5.8
Palpitation	7	4.5
Tinnitus	4	2.6
Insomnia	4	2.6
Numbness and tingling	4	2.6
Weakness	2	1.3
Nervousness	1	0.6

The frequency of symptoms (Table II) is no indication of the subjective distress of the individual. Angiospasm, fainting and epistaxis, which were relatively rare occurrences, caused the patients more discomfort and worry than did the other symptoms. Aches and pain, dizziness, tinnitus and insomnia were also very troublesome while the remaining symptoms caused comparatively little distress.

The Complaints of Patients With Conditions Related to Hypertension. The presentation of the symptomatology of hypertension cannot be considered complete until an attempt is made to answer three questions. First, are symptoms specific for hypertension? Second, is the symptomatology due to the elevated blood pressure or is it the expression of some underlying condition which may or may not be related to the development of the high arterial tension? Third, is there any specificity in the symptoms exhibited by patients with hypertension? In order to answer these questions an analysis was made of the clinical histories of patients diagnosed as suffering from the following six conditions: chronic constipation, obesity, hypertrophic arthritis, menopause, menopause hypertension and psychoneurosis. These conditions were responsible for all the complaints and physical findings of the patients.

Chronic Constipation was chosen because, like hypertension, it represents a common condition found in individuals who tend to be mild chronic invalids. The symptomatology listed in Table VII is based on a study of the records of 96 consecutive cases of uncompli-

TABLE VII.—SYMPTOMS WITH AN INCIDENCE OF MORE THAN 10 PER CENT OCCURRING IN GROUPS OF PATIENTS WITH CHRONIC CONSTIPATION, OBESITY, CHRONIC HYPERTROPHIC ARTHRITIS, PSYCHONEUROSIS, MENOPAUSE WITH NORMAL BLOOD PRESSURE AND MENOPAUSE WITH HYPERTENSION.

Chronic constipation (96 cases).		Obesity (95 cases).		Hypertrophic arthritis (59 cases).		Psychoneuritis (120 cases).		Menopause with normal blood pressure (213 cases).		Menopause with hypertension (96 cases).	
Symptoms.	Percentage frequency.	Symptoms.	Percentage frequency.	Symptoms.	Percentage frequency.	Symptoms.	Percentage frequency.	Symptoms.	Percentage frequency.	Symptoms.	Percentage frequency.
Abdominal pain	52.1	Aches and pains	46.3	Aches and pains	98.3	Aches and pains	39.1	Aches and pains	48.8	Headache	53.1
Headache	38.5	Dyspnea	29.5	Nycturia	16.9	Headaches	34.1	Hot flashes	43.7	Dizziness	46.8
Gas (belching or flatulence)	26.1	Headache	26.3	Dyspnea	11.9	Dizziness	26.6	Headaches	38.0	Aches and pains	44.7
Nausea	22.9	Dizziness	13.7	Headache	11.9	Nervousness	24.1	Dizziness	33.8	Hot flashes	43.7
Dyspnea	19.8	Edema	11.6			Dyspnea	21.6	Nervousness	31.9	Dyspnea	27.1
Aches and pains	18.8	Nycturia	10.5			Palpitation	15.8	Dyspnea	24.4	Nycturia	21.9
Dizziness	16.7					Weakness	15.0	Nycturia	18.3	Nervousness	16.6
Palpitation	13.5					Nycturia	11.7	Weakness	16.5	Tinnitus	14.6
Abd. distention	12.5					Insomnia	10.8	Palpitation	13.6	Weakness	13.5
								Insomnia	10.3	Palpitation	11.5

cated chronic constipation with normal blood pressure. In general the symptomatology of chronic constipation was totally unlike that of hypertension.

Obesity. The typical patient with high blood pressure often is described as being overweight, if not actually obese. For this reason, the symptomatology of 95 consecutive patients with normal blood pressures who were suffering from no other condition save obesity, was determined. The results are presented in Table VII.

These patients complained of pains and dyspnea about as frequently as did those with hypertension.

Chronic Hypertrophic Arthritis. The symptomatology of this condition is presented in Table VII. The 59 case records examined represent only uncomplicated cases with normal blood pressures. Aches and pains were practically universal complaints but these pains were almost always (70 per cent) sharply limited to the region of the joints and rarely radiated or migrated to other parts of the body as was the case in patients with hypertension. In addition 50 per cent of the cases with arthritis showed the pains to be definitely related to motion. The remaining symptoms are similar to those seen in cases of high blood pressure but they were relatively infrequent complaints.

Menopause and Menopause Hypertension. During forty-two months, there were treated in the medical outpatient department 96 women who were diagnosed as in the menopause period and who were discovered to have hypertension. During the same period of time there were 213 women with normal blood pressures who were treated because of symptoms believed to be due to the menopause. The symptomatology of menopause hypertension (Table VII) is essentially the same as that of uncomplicated hypertension (Table II). The outstanding difference is in the frequency with which patients complain of hot flashes.

The symptomatology of uncomplicated menopause (Table VII) shows some differences from menopause associated with hypertension. Nervousness and insomnia occurred more frequently in women with normal blood pressures than in women with hypertension; tinnitus, on the other hand, was a less frequent complaint. Despite these differences, the individual case histories of menopause, menopause hypertension and uncomplicated hypertension are frequently indistinguishable from each other. It was not uncommon to discover a patient with normal blood pressure, having symptoms attributed to menopause, who later developed hypertension and who showed no change in symptomatology. There were an equal number of cases with both menopause and hypertension whose symptomatology persisted despite a subsequent diminution in the arterial tension to a normal level.

Psychoneurosis is another condition the symptomatology of which is similar in many respects to that of hypertension. The

points of difference between the two conditions are as follows: in 30.8 per cent of 120 consecutive cases of uncomplicated psychoneurosis, with normal blood pressure, there was discovered an underlying psychic conflict which may have been the basis for the condition. Both headaches and dizziness were frequent complaints but they occurred together only two-thirds as frequently as they did in hypertensive patients. Nervousness, insomnia, gastrointestinal complaints and numbness and tingling were found more frequently among psychoneurotic than among hypertensive patients, while nycturia and epistaxis were relatively infrequent symptoms. In addition, there were a variety of unusual complaints which could not be explained on an organic basis. These included such symptoms as sex impotence, aphonia, and anesthesia. It is mainly on the basis of such complaints that histories of psychoneurotic patients can be separated from those of individuals with hypertension, and yet there are many individual records which are so similar that the differential diagnosis cannot be made without the sphygmomanometer.

Discussion. Headaches, dizziness, aches and pain, dyspnea and nycturia alone or in combination were by far the most frequent complaints of the patients with arterial hypertension. Epistaxis and migraine, in contrast to observations made by others, were noted rather rarely. Complaints identical to those observed in patients with hypertension were present in a large proportion of the patients with obesity, menopause and psychoneurosis whose blood pressure was normal. Vasomotor disturbances in patients with obesity, menopause and psychoneurosis are common. It is also recognized that in the early stage of hypertension considerable fluctuation in the systemic blood pressure occurs. This fluctuation in the blood pressure is an expression of the changes in the peripheral arteriocapillary system which is regulated by the vasomotor center.[5] Even in the later stages of hypertension when the blood pressure becomes more fixed, the cerebral circulation may be disturbed because of the presence of an increased arteriolar resistance and hence disturbed capillary circulation. The vasomotor disturbances in the circulation are the common explanation for similar symptomatology in hypertension, obesity, menopause and psychoneurosis. The symptoms of patients suffering from arterial hypertension cannot, therefore, be considered as specific or characteristic. It is also questionable whether the high arterial tension in itself is responsible for the symptoms, because no relationship could be demonstrated between the height of blood pressure and the severity of the complaints. In a considerable number of patients greatly elevated blood pressure was present without symptoms.

In Table VIII the symptoms of hypertension are arranged according to their probable anatomic source. A number of symptoms are placed under more than one heading, because the etiology may be

multiple. The majority of symptoms are referable to the disturbance of the central nervous system. Some of them, as hot flashes, angiospasm, throbbing, are the direct results of vasomotor changes in the cerebral vessels, while others may result indirectly from the effect of the changed cerebral circulation on the functions of certain regions of the brain. It is of interest that all the complaints referable to the heart and kidneys, with the exception of hematuria, may also result from vasomotor disturbances of central origin.

TABLE VIII.—SYMPTOMATOLOGY OF HYPERTENSION ARRANGED ACCORDING TO POSSIBLE ETIOLOGY.

Cerebral.	Cardiac.	Renal.	Other vascular areas.
Headache	Dyspnea	Nycturia	Epistaxis
Dizziness	Palpitation	Edema	Muscular cramp
Aches and pains	Weakness	Hematuria	Hemoptysis
Dyspnea	Cardiac pain		Weakness
Nycturia	Edema		Aches and pains
Nervousness			
Palpitation			
Tinnitus			
Weakness			
Insomnia			
Precordial pain			
Numbness and tingling			
Vague ocular symptoms			
Hot flashes			
Nausea or vomiting			
Angiospasm			
Throbbing			
Fainting spells			

The similarity of symptoms in patients with arterial hypertension, menopause, obesity and psychoneurosis does not, *a priori*, justify the conclusion that menopause, obesity and psychoneurosis are in etiological relationship to arterial hypertension. Nevertheless, it is more than a coincidence that two of the three conditions, namely, menopause and obesity, are frequently associated with hypertension. The relationship between psychoneurosis and arterial hypertension is probably closer than is recognized at present. Psychic trauma and conflict, abnormal sensitivity of the psyche, as well as the constant strain of life, play most important rôles in the development of psychoneurosis. These factors probably are often responsible for the development of hypertension and therefore the elimination of these psychic conditions plays a primary rôle in the prevention and treatment of hypertension.

Summary and Conclusions. 1. An analysis of the complaints of 1090 ambulatory patients with primary (essential) hypertension indicates that the following symptoms are present in more than 20 per cent of the cases: headache (43.3 per cent), dizziness (40.3 per cent), "aches and pains" (38.7 per cent), dyspnea (27.7 per cent), nycturia (25.9 per cent).

2. Epistaxis and migraine were infrequent symptoms.

3. Arterial hypertension is not associated with characteristic symptomatology. Almost all the symptoms of patients with arterial hypertension are referable to a disturbance of the central nervous system and are expressions of a disordered vasomotor system.

4. Among conditions with normal blood pressure, menopause, obesity and psychoneurosis showed symptoms similar to those of arterial hypertension. All four conditions frequently exhibit vasomotor instability.

5. Psychic conditions may play a more important rôle in hypertension than is realized, and therefore should be considered in treating the disease.

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VISCEROPTOSIS: ITS CLINICAL SIGNIFICANCE AND TREATMENT.

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In 1885 Franz Glénard first described the condition now known as visceroptosis. Since that time numerous articles by Rovsing,[1] Goldthwait,[2] Coffey,[3] Martini,[4] Mills[5] and others have appeared in the literature emphasizing the importance and various phases of this condition. Following the epochal discovery of the Roentgen ray by Wilhelm Roentgen in 1893 with its subsequent usefulness in examination of the gastrointestinal tract, conceptions of the normal position which abdominal viscera occupy have been broadened. Anatomists described the position of organs with the subject in the supine state. Variability in size, shape and location appears to be the rule rather than the exception, especially with the relatively movable gastrointestinal tract. In 1923 Moody, van Nys and Chamberlain[6] studied 300 men and 300 women, all presumably normal, taking Roentgen rays with the subjects in the upright posture. They concluded that the normal position of the stomach is lower than generally believed and that the term "gastroptosis" is

seldom justifiable. Practically all observers are agreed that the stomach and colon occupy a lower position in the female than in the male due to inferior musculature and ligamentous support. Before we label any position abnormal it is necessary to know the normal variations. Chamberlain[6] and his associates found the greater gastric curvature 1 inch below the interiliac line in 4 per cent of male and in 10 per cent of female patients. We may look upon variation from two different angles.

There is constitutional variation, that is to say, a long stomach is the rule in a long body. The stomach fits the individual, so to speak; there is, also, individual variability. In either type stretching, elongation, relaxation, dilatation, or fixation by adhesions may develop. It is in this latter class that clinical symptoms may occur. The well-being of the individual is dependent to a considerable degree upon the integrity and proper function of the abdominal viscera. The gastrointestinal tract holds a large proportion of the blood. French authors have termed it the "coeur abdominal." Any marked distention, drag, relaxation or other alteration which interferes with the optimum function of this tract may have far-reaching effects on the individual.

The constitutional type known as "visceroptotic habitus," "maladie constitutionelle" of the French, or "allgemeine Krankheit" of the Germans with malnutrition, narrow and flat thorax, acute costal angle, pot belly, hypotension and nervous disposition is common in all clinics and is easily recognized. These individuals frequently describe themselves as being "not sick or not well." Any one or all of their body systems are below par although complaints ordinarily point to either the gastrointestinal or cardiovascular tracts as the weakest links in the chain. Goldthwait[2] believes the condition is nearly always hereditary in these patients and maintains that the Mendelian law of inheritability of characteristics may be as true for the shape and position of the stomach as for the color of the eyes. Inheritance of a ptotic habitus renders the individual susceptible to a multitude of physiologic interruptions and aberrations which may give rise to a condition of chronic invalidism. These cases are easy to diagnose. Concerning their existence there is no controversy. Radiographic studies uniformly reveal a long, atonic stomach with its greater curvature deep in the pelvis. The colon, cecum, and one or both kidneys are likewise ordinarily in low position. It is improbable that the positions these organs assume would fall within normal variations.

In contradistinction to the class of patients just described, there exists a second large group in which no external factors lead one to suspect a disproportion between the body type and the shape and size of the stomach.

In a series of 100 cases studied in the Lankenau Hospital Medical Clinic we have interpreted the types as follows:

TABLE I.—TYPES OF VISCEROPTOSIS.

A. Congenital, 27 Cases.

1. Primary. Defect more pronounced and symptoms usually arise early in life.
2. Potential. Patients more nearly normal, that is, with better development of mesenteric supports. Symptoms may or may not arise, depending on resistance of individual and force of exciting circumstance.

B. Acquired, 73 Cases.

Secondary. Diseases, overwork. Repeated pregnancies, loss of weight, and so forth.

The age incidence and sex are shown in the following tables:

TABLE II.—AGE INCIDENCE.

Years.	No. cases.
10 to 20	4
20 to 30	32
30 to 40	16
40 to 50	24
50 to 60	20
60 to 70	4

TABLE III.—SEX.

Female.		Male.	
Single	22	Single	8
Married	46	Married	24

These patients offer an infinite variety of complaints.

In the series studied in the Lankenau Hospital Medical Clinic the majority of patients gave as their chief complaint some symptom referable to the upper or lower gastrointestinal tract; a smaller number presented symptoms pointing to the pelvis or lower spine. In the table below a complete analysis of the chief complaints offered by 100 cases, is presented.

TABLE IV.—ANALYSIS OF CHIEF COMPLAINTS IN 100 CASES.

	Per cent.		Per cent.
Gas	71	Pelvic distress	12
Constipation	63	Insomnia	12
Upper abdominal distress	49	Nausea and vomiting	12
General weakness	32	Dysmenorrhea	5
Swelling of stomach	30	Pain in chest	3
Nervousness	30	Diarrhea	3
Lower abdominal distress	28	Mucous stools	1
Backache	18	Bloody stools	1
Headache	15	Palpitation	1

Patients may or may not reveal disturbances of one or more of the major systems of the body. They are not of necessity undernourished, in fact, many are overweight, and Roentgen rays of the gastrointestinal tract are usually deemed unnecessary. If examined by Roentgen ray, the organs may be found in low position but the

prolapse may not be much beyond the extent of normal variation, that is to say, some point near the interiliac line. Tone is usually reduced.

It is chiefly this group of patients that has been studied intensively because the ordinarily prescribed modes of treatment have not given relief.

While a majority of the patients examined were found to be undernourished it is interesting to learn that 15 per cent were overweight. Focal infections are common in this class of patients, 26 per cent possessing a nidus somewhere in the sinuses, teeth, nose or throat. An unusually large proportion of patients in our group were found to have an erythrocyte count below 4 million.

It is worthy of note that 62 cases showed a diminished gastric acidity and 18 per cent exhibited an excess of acid in the gastric secretion.

Studies of the tonicity of the gastric musculature were made by Shoemaker. The basis of judgment of the gastric tonicity was the manner in which the stomach wall maintained a barium column of 500 cc. Hypertonicity was said to exist when the column was high and narrow; hypotonicity, when the lower half dilated and appeared flabby. The latter condition was found in 62 per cent of cases.

Lower bowel stasis is one of the most frequent accompaniments of visceroptosis. In our series 83 cases presented this sign.

TABLE V.—CHIEF PHYSICAL FINDINGS IN 100 CASES.

	Per cent.		Per cent.
Undernutrition	69	orthotonicity	33
Normal weight	16	hypertonicity	5
Overweight	15	Stasis	83
Focal infections (nose, tonsils, teeth)	26	Duodenal deformities	6
Anemia (below 4 million red blood cells)	40	Mobile cecum	82
Hypotension	22	Mucus in stool	10
Hypertension	12	Reduction of renal phenolsulphonephthalein output below 40 per cent in two hours	8
Gastric hypoacidity	62	Relaxed pelvic floor	29
Gastric hyperacidity	18	Thyroid enlargement	19
Gastric musculature (by fluoroscope):		Arthritis	8
hypotonicity	62	Basal metabolism decrease (of 24 patients)	20

Many were operated upon for appendicitis, cholecystitis, peptic ulcer, pelvic disease, intraäbdominal bands or adhesions and other lesions.

TABLE VI.—OPERATIONS.

For.	No. cases.	For.	No. cases
Fibroid uterus—hysterectomy	2	Goiter	3
Chronic appendicitis	18	Varicose veins	1
Gastric ulcer	1	Tubo-ovarian disease	6
Duodenal ulcer	1	Herniorrhaphy	1
Pelvic operations (type not designated)	2	Nephrectomy	1
Cholecystitis	6	Hydrocele	1
Uterine suspension	2	Hemorrhoids	1

This table indicates the variety of operations performed on cases previous to knowledge of a ptotic bowel. Inattention to the latter condition explains, in many cases, incomplete postoperative recovery. If the lesion sought was found and removed, improvement but incomplete relief occurred. Infrequently the laparotomy was of no avail.

In surveying these cases one is forced to consider the possibility of ptosis of one or more intraäbdominal organs as a contributing element to the patient's distress. It is comparatively rare to find a fallen liver or spleen, whereas, ptosis of the right kidney, the cecum and transverse colon is common.

TABLE VII.—ABDOMINAL ORGANS INVOLVED IN 100 CASES.

	Per cent.
Stomach	91
Transverse colon	88
Right kidney	3
Left kidney	1
Liver	2
Spleen	0

Additional lesions in the pelvis were present in the following proportions:

TABLE VIII.—CASES WITH ACCOMPANYING LESIONS OF PELVIS IN A SERIES OF 100 CASES.

	Per cent.
Uterine displacement	8
Lacerated cervix	32
Relaxed vaginal wall:	
(*a*) Cystocele	16
(*b*) Rectocele	2
Ovarian and tubal lesions	12

Ptosis frequently exists in association with the major diseases. Its presence may be the result of these lesions or may occur incidentally. In one patient with asthma, immediate and sustained relief from the asthma was obtained by correction of the visceroptosis.

TABLE IX.—ADDITIONAL DIAGNOSES IN A SERIES OF 100 CASES.

	Per cent.
Asthma	2
Hay fever	1
Pituitary dystrophy	1
Chronic pulmonary tuberculosis	2
Syphilis (Wassermann and Kahn 2, 3, or 4+)	10
Heart disease	8
Sciatica	11
Gastric ulcer	2
Duodenal ulcer	2
Pelvic disease	15
Chronic nephritis	7
Thyroid disease	5
Chronic cholecystitis	6
Mucus colitis	1

With the solid viscera and the transverse tube, displacement of the entire organs occurs. With the stomach a different condition arises. Its size, contour, and relative position depends on its contents, muscular tone and nerve integrity upon the presence or absence of gas, on the intraäbdominal pressure, on the position, and contents of other organs, chiefly the large bowel, and on the body posture, osseous and muscular development and general nutrition. Since the stomach is fixed at the cardia and below the pylorus, it is obvious that prolapse of this viscus does not occur. Rather does it become elongated or dilated from lack of tone. The term "gastroptosis" is a misnomer. Gaston Lyon[7] has suggested "vertical dislocation" while Martini and Comas[4] propose "dolicogastrie" as a more correct designation. The latter term appears to fit the condition more suitably than others so far offered.

The opinions of twenty of the leading radiologists in four different countries were requested on the following five points:[8]

1. What, in your opinion, constitutes gastroptosis?
2. Is it important clinically?
3. Is it common?
4. When is, and when is not an elongated stomach ptosed?
5. To what are symptoms due, when present?

In answer to the question, "What constitutes gastroptosis?" the following impressions were given:

(*a*) Prolapse of stomach as part of enteroptosis, only.
(*b*) An organ which suggests drag on its attachments.
(*c*) A relative elongation out of proportion to body habitus.
(*d*) Greater curvature below left iliac crest.
(*e*) Vertical elongation associated with atony and dilatation.
(*f*) Pyloric sphincter appreciably below iliac crest.
(*g*) Elongation of stomach with descent of distal third of greater curvature.

In response to the question concerning the clinical importance of gastroptosis, 4 men reported in the affirmative, 3 in the negative, and the others believed its importance was associated with that of enteroptosis from which symptoms due to gastroptosis alone could not be separated.

Eight of these radiologists look upon gastroptosis as a common condition and two regard it as uncommon. The remaining answers were evasive.

To the question "When is, and when is not an elongated stomach ptosed?" the majority conclude the diagnosis of ptosis can be made when the stomach length is out of proportion to the body type. One investigator states ptosis exists when the sphincter is below the iliac crest; another designates ptosis when greater curvature descends more than one-third the distance between the anterior iliac spine and symphysis pubis; the remaining observers held it to be a matter of personal opinion.

To the last question regarding cause of symptoms, these responses were given:

(*a*) Drag on duodenum.
(*b*) Tension.
(*c*) Stasis.
(*d*) Drag on mesentery with its resultant irritation to the sympathetic and vagus nerves.
(*e*) Duodenal stasis with its resultant toxic absorption.
(*f*) Compression on mesenteric artery.
(*g*) Tension on bloodvessels, lymphatics, and to absence of support to the under surface of diaphragm.
(*h*) Delay in emptying with gas and distention.
(*i*) Mechanical interference plus disturbed gastric chemistry.

Developmental and Anatomic Considerations. Searching for the basis of signs and symptoms leads to a brief consideration of the embryology of the digestive tract and its supports. In the early stages of development the primitive gut is a straight tube. By an outpouching and elaboration of layers and glandular elements, the stomach is formed from the foregut. It is maintained in position chiefly by the mesenteric reflections, namely, the gastrophrenic and gastrohepatic ligaments and the continuation of the gut.

The entire large bowel develops from the caudal part of the primitive gut. By rotation and the formation of an inverted U anterior to the loops of the small intestine, the large bowel assumes its final position. The mesentery usually covers the anterolateral aspects of the rectum, sigmoid, descending colon and ascending colon, whereas, the transverse colon is entirely surrounded by peritoneum. Variations in these attachments explain many cases of mobile and prolapsed large bowel. Stable position and retention of viscera are not completed at birth. Victor[9] has attempted to average the individual mesenteric variations and find an anatomic mean. Suffice to state that right here may be found certain important factors in the production of prolapse of the large bowel and cecum. Furthermore, there are five anatomic points which predispose to later kinking, mechanical obstruction or stasis, the foundation for troublesome constipation. These points are:

1. Near the left psoas at the pelvic brim.
2. Just proximal to the splenic flexure.
3. In the subpyloric region of the transverse colon.
4. Proximal to the hepatic flexure.
5. Cecum.

With full rotation and complete fusion of the mesentery it is impossible for ptosis to occur unless these attachments become weakened, then stretched. We know this takes place in cases of debilitating disease where loss of weight is the rule. This is acquired ptosis.

TABLE X.—IMPORTANT FACTORS IN PRODUCTION OF VISCEROPTOSIS.

1. Heredity.
2. Lack of exercise: Defective muscular development in childhood years.
3. Defective posture.
4. Embryonic defects of rotation and development. (Gastrointestinal tract.) (Mesenteric variations.)
5. Loss of weight.
6. Repeated pregnancies.
7. Debilitating diseases.
8. Overwork. Worry.
9. Lack of exercise: Overeating in adult years.
10. Weakening of abdominal wall by operation.

The abdominal cavity is spacious and roomy just beneath the diaphragm where the large viscera are found. Normally the lower ribs flare outward, the diaphragm arches upward, and the vertebral column has a gentle backward bow which curves forward at the lumbosacral level to produce, with the psoas muscles, a prominence or shelf on which the upper abdominal organs rest. The anterior muscles and aponeuroses complete the encasement.

The muscular osseous system or external sac, so-called by Bourcard[10] incloses the digestive tube or internal sac. Between the two systems which may be conceived as acting in opposition, a condition of negative pressure is created. This pressure is an important adjunct in holding the organs in place and relieves the mesenterics of considerable strain:

1. Tonicity of abdominal wall.
2. Atmospheric pressure.
3. Extraperitoneal and mesenteric fatty tissue.
4. Tonicity of involuntary musculature of the gastrointestinal tract regulated by involuntary nervous system.
5. Fluid and solid contents of digestive tract.
6. Gaseous contents of digestive tract.

Thus a condition of intraäbdominal equilibrium is established. Disturbance of this balance will tend to atony and dilatation of the digestive tract. Interference with circulation and pressure on involuntary nerves impairs the function of the viscera leading to poor alimentary hygiene, digestive disorders, constipation, etc. Faulty posture with relaxation of abdominal muscles, lowering of the anterior chest wall, loss of weight, for example, all tend to increase the intraäbdominal negative pressure thereby placing a greater tension on the mesenteric attachments. Sagging of the large bowel with ofttimes a band or adhesion producing a constriction, the basis for excessive fermentation and therefore gas, dilatation and atony of the gastric wall with stretching and sagging set the stage for the clinical drama. If all of the organs descend, function may pre-

sumably continue without any major manifestations of impairment since their relative positions remain the same.

TABLE XI.—PROBABLE IMPORTANT FACTORS IN PRODUCTION OF SYMPTOMS.

1. Chronic obstruction.
2. Stasis.
3. Defective circulation of abdominal organs.
4. Pressure on involuntary nerves by sagging viscera.
5. Drag on common bile duct, portal vein, and hepatic artery.
6. Influence on secretion of digestive juices and ferments.
7. Pelvic pressure.

Usually mesenteric relaxation is not uniform, or, adhesions fix certain regions of the bowel in position while other portions prolapse. This is the basis for chronic obstruction with stasis and toxic absorption. Sir Arbuthnot Lane[11] has recommended colectomy for these cases pointing out that, by removal of a section of the large bowel toxic absorption is minimized. Sir Arthur Keith,[12] however, believes the stasis is due to dysfunction of the sympathetic nervous system. It is probable that both conditions play a part in causing stasis, stercoremia, and the clinical picture.

Differential Diagnosis. Visceroptosis clinically may resemble any abdominal condition in the acute or chronic stages. Many patients suffer from pain in the right upper quadrant. In the series here presented six individuals had had more than two attacks of typical biliary colic.

As seen in Table VI it is not infrequent that the patient has had a previous appendectomy with no relief.

Many German surgeons and radiologists note an intimacy between the occurrence of peptic ulcer and gastroptosis. Pelvic inflammatory disease is not infrequently present in ptotic patients. Goldthwait and others have found arthritis and rheumatic tendencies twice as frequent in patients with ptosis, as in nonptotic cases.

The difficulty in the diagnosis of ptosis is that it is too easy. So many patients have suffered for years from fallen organs and one often impatiently classifies them as "neurasthenic."

TABLE XII.—RESULTS OF TREATMENT IN 100 CASES.

	Per cent.
Improved	82
Unimproved	18

The treatment of no class of patients can produce more gratifying results or prompter relief than in this group. Though percentage of improved patients in our series may appear low, complicating conditions, as shown in Table XIII, may, in part, offer an explanation.

Unimproved cases in the series here presented, in certain individuals showed additional lesions (which in themselves may have been primary) as the following table shows:

TABLE XIII.—COMPLICATING FACTORS IN UNIMPROVED CASES OF 100 CASES STUDIED.

Chronic pulmonary tuberculosis	2 cases
Chronic heart disease	4 cases
Nephritis	3 cases
Thyroid disease	1 case
Pelvic disease (with adhesions)	5 cases

Treatment: 1. Prophylaxis.

2. Adequate care for coëxisting lesion, if present.

3. Removal of infective foci, chiefly in respiratory and pelvic tracts.

4. Elimination: Bowels, kidneys, skin, lungs.

5. Rest.

6. Diet.

7. Massage.

8. Exercise.

9. Abdominal support (belt, adhesive strapping, and so forth).

10. Medicine.

11. Surgery.

12. Advice about future precautions.

Goldthwait[13] suggests attention to posture in school clinics as the proper prophylaxis for potential ptotic disorders.

The alleviation of symptoms requires treatment of a broad scope, suitable to the individual requirements of each patient. The time-consuming element in handling this large group of patients is in the search for the basis of the complaints. It takes time, occasionally doctors are impatient and the patient finally gravitates to the cults for relief.

By and large, the younger and more pliable the patient the more is to be expected from treatment. The utmost coöperation by the patient is likewise necessary. Institution of the proper therapeutic measures gives immediate relief in approximately 40 per cent of cases, but treatment, in order to be effective, must be followed over an extended period of time.

Treatment should aim to:

1. Return the organs to their normal position.
2. Improve the tone of the voluntary and involuntary nervous system.
3. Correct the posture.
4. Increase weight when necessary.
5. Inform the patient of the nature of the condition and outline precautions to avoid future disability.

In our experience less than 5 per cent of cases require hospitalization.

With the case thoroughly studied it is wise to explain to the patient in detail the nature of the condition and the rationale of treatment.

Hygienic measures including complete elimination through the bowels, kidneys, skin and lungs with rest of ten to twelve hours at night; two hours in the afternoon, and forty-five minutes lying on the left side after each meal to facilitate digestion and rest the mesenterics, are important. We prescribe a vigorous general massage twice daily using cocoa butter or oil of wintergreen.

Exercises directed to increasing the strength of the abdominal muscles, especially, and at the same time to raise the sunken chest and augment the diaphragmatic excursion are advised twice a day.

Foci of infection located usually in the teeth, tonsils, nares, sinuses, or pelvic tract are cleared up.

Diet is of primary importance. If the patient is suffering from an acute digestive rebellion it is wise to withhold all food for twenty-four to forty-eight hours. Frequent alkaline gastric lavage favors relaxation of the spasm and soothes the irritated mucosa. Fortunately this condition is not common.

Reflecting upon the nature of the stomach in these cases furnishes important information in outlining the diet. Four or five small meals are usually better tolerated than three large ones. As a rule it is prudent to administer fluids between meals. Immediately following ingestion patients should lie down, resting on the left side since this facilitates peristalsis and pyloric passage. The type of food is selected according to the needs of the individual. Obese patients should reduce and undernourished ones increase in weight.

The question of a mechanical support is one of the bugbears in the treatment of fallen viscera. Improper belts, improper adjustment of the correct type of belt, neglect to check up frequently by the fluoroscope, and, finally, permitting the patient to wear the support indefinitely, all add to, rather than alleviate, the discomfort. Probably no single therapeutic measure in the entire field of medicine has been so bungled as this of supports for ptosis cases. Not infrequently doctors have made the correct diagnosis but failed to lead the patient carefully over the correct road to relief.

Wearing a belt constantly has certain disadvantages. It is often uncomfortable and always is at first. It tends to weaken and destroy the strength of the abdominal muscles. Unless the advantages outweigh these possibilities the support is pernicious.

Innumerable corsets, binders, belts, stays, pads, supports and strappings have been tried.

About ten years ago Page constructed a support which consists of two connected vertical bars fitting over the sacrum with a stiff curved rod extending around either iliac crest, bent in such a way as to maintain in the suprapubic region a hard, oval leather pad. This has proven satisfactory. Each patient is fitted; then, following barium,

a check up is made with the fluoroscope. Not infrequently the transverse colon will slip down behind the pad unless the utmost precautions are followed. Once properly adjusted and the patient well informed concerning the manner in which it is put on while lying down, there should be a fluoroscopic check-up each week for one month and after that at monthly intervals. As soon as the tone and position of the stomach and colon are normal the belt should be replaced by a soft abdominal binder. Abdominal massage twice daily is advised to build up the abdominal muscles.

Numberless patients today are wearing belts which have outstayed their welcome.

Medicines to stimulate the appetite, to improve gastric secretion, and facilitate digestion are useful. Any of the tonics may be prescribed. In addition to these, atropin, following meals, is useful to assist in passage through the pylorus. We also routinely prescribe some combination of malt and cod-liver oil with orange juice. Oscodol has recently been tried with satisfactory results.

Neurotic patients often require a mild sedative during the early stages of treatment.

Less than 10 per cent of cases will require surgical intervention. Those with associated pathologic conditions of the stomach, biliary tract, bowel or pelvic region and, also, when thick adhesions hold the organs out of position, will not respond to conservative measures. It is important to keep in mind the indicated postoperative care these cases require.

With each patient informed of the nature of his condition and properly advised about the future, the chances for recurrence should be reduced.

In conclusion, we believe that the possibility of visceroptosis should be considered in each case that presents abdominal symptoms. Consider the vast number of persons who are below par, those who are neurasthenics, or chronic invalids. One wishes to dispel the thought. They are uninteresting. They are floaters from one doctor to another, from one hospital to another.

The medical profession does not appear to be impressed with the subject of visceroptosis. Patients submit daily to operations with the hope that they may be relieved. Investigation disposes one to conclude that, except for extraneous environmental and social problems of adaptability and compatibility, the greater proportion of these troublesome complainers are afflicted with some one or several of the stigmata designated as ptosis. This discussion attempts merely to focus the attention of the profession on the condition in the hope that more information may be obtained regarding the essential nature of the problem, and more satisfactory and efficient modes of treatment be revealed.

The distress of these patients is our problem. They deserve the best efforts of the best minds of our guild.

Summary. 1. Visceroptosis is a condition of downward displacement of the abdominal viscera that may exist in individuals who appear to be in perfect health.

2. The condition may be primary, that is, hereditary, or it may be acquired following somatic devastation from overwork, repeated pregnancies, prolonged disease, and so forth.

3. In a series of 100 cases studied in the Lankenau Hospital Medical Clinic the chief symptoms have been analyzed here. They usually pointed to the gastrointestinal tract.

4. Satisfactory therapeutic measures depend upon a consideration of the cause of the symptoms.

5. In the Lankenau Clinic a definite daily program is planned for each patient including proper diet, elimination, rest, massage, and when indicated, mild sedatives. All foci of infection are eradicated and, in selected cases, a Page abdominal support is applied. In a small percentage of cases requiring surgical intervention the fundamental rationale of the treatment should not be neglected.

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A TUMOR OF THE ADRENAL GLAND WITH FATAL HYPOGLYCEMIA.

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Shortly after the discovery of insulin by Banting and Best, the symptoms of hypoglycemia or hyperinsulinism became known to all physicians and many patients who used insulin. The symptoms

described then under the head of "insulin shock" or an overdose of insulin were weakness, nervousness, a "trembly feeling," slight confusion, rapid pulse, muscle twitching, profuse sweating, stupor, convulsions and coma. The severity of the symptoms, of course, was in direct proportion to the degree of hypoglycemia.

In 1924 Harris,[1] reasoning that various endocrine glands exhibited states of increased or diminished function, for example, the thyroid and pituitary glands, conceived the idea that the pancreas, theoretically at least, might under certain conditions show both a hypofunction and hyperfunction of its endocrine portion. Diabetes mellitus already having been thoroughly established as an example of hypoactivity of the islet cells, it only remained for him to find cases that demonstrated overactivity of the islet cells to substantiate his idea. Being on the lookout for such cases, he soon found some exhibiting symptoms of hypoglycemia; these, he thought, were due to overactivity of the islet cells and he gave the name hyperinsulinism to them. His cases gave symptoms of mild hypoglycemia which came on three to four hours after meals and were relieved by eating food. He believed, as does Jonas,[2] who gives an excellent review of the literature on hypoglycemia, that when the blood sugar dropped below 0.07 per cent symptoms of hypoglycemia manifest themselves.

While, no doubt, there are some cases of hypoglycemia accompanied by hypoglycemic symptoms due solely to hyperfunction of the island cells, all cases of hypoglycemia are not so easily explained; for, as Harris has pointed out, it also seems probable that disorders of the islet cells may be associated with dysfunction of the thyroid, the pituitary bodies, the adrenals and other organs of internal secretion.

Hartman,[3] in a recent review of hypoglycemia, in addition to the endocrine dysfunctions, mentions progressive muscular atrophy, acute yellow atrophy of the liver, extreme physical action and tumors of the pancreas as additional causes for hypoglycemia.

Nor is the problem concerning the cause of hypoglycemia so simple as it may seem theoretically, as pointed out by a recent editorial writer:[4] "The primary factors responsible for the change in the blood-sugar level may be either failure of the liver activities in liberating sugar or overfunction of the pancreas." It is a well-known fact that extracts from the pituitary bodies and adrenals play a part in mobilizing blood sugar. Although many German writers regard hypoglycemia an important feature in Addison's disease, and although Snell and Rowntree[5] state they have noticed it in a few of their cases as a terminal phenomenon, the latter authors agree with Rosenow and Jogrettis that it is not a pathognomonic sign, nor even constant in its occurrence.

Stewart,[6] in intensive studies on the function of the adrenals, found a low blood sugar only as a terminal factor in cases where

the cortex of the gland was destroyed. A further interesting observation which Stewart made and one that might have some bearing on the case herein reported was that when the cortex of the adrenals was destroyed the postmortem findings showed in practically every case marked hyperemia of the pancreas. Mochling's[7] experiments led him to the conclusion that aplastic states of the pituitary gland are concomitant with aplasia of the suprarenal cortex and conversely, hyperplasia of the pituitary gland results in hyperplasia of the suprarenal cortex. Mochling's findings may also have a possible bearing on the present case.

Recently there have been reported a number of very interesting cases of hyperinsulinism or hypoglycemia due either to simple or overactivity of the islet cells, as in the case of Finney and Finney[8] and in Case 2 of Allen's;[9] or to overactive islet cells accompanied by tumors of the islet cells as in the following four cases:

The first case was reported by Wilder, Power and Robertson.[10] A patient, aged forty years, three years prior to admission, showed some sugar in the urine. Symptoms had been present characterized by sudden attacks of faintness and weakness, numbness of the tongue and lips for eighteen months. For the past few months they had been more frequent and more severe. Profuse sweating and trembling have also been present. Eating and sweet drinks prevented attacks. Body weight dropped from 170 to 117 pounds. Intravenous glucose caused the blood sugar to rise in one-half hour from 85 to 218 mg. and traces of sugar were found in the urine. Three hours later the blood sugar dropped 131 mg. Epinephrin did not produce any effect toward mobilizing the blood sugar; neither did the pituitary gland extract. Twenty grams of glucose per hour were necessary to keep the blood sugar normal. Carcinoma of the tail of the pancreas was found at autopsy, and metastases to the liver. Carcinoma arose from the island cells of the pancreas.

The second case was reported by Thalhimer and Murphy.[11] A white woman, aged fifty-seven years, about two and a half years before admission, had attacks characterized by somnolence, restlessness and irritability. These attacks varied from two weeks to two months at first, but during the last year averaged about three a week. Epileptiform convulsions were present during the latter attacks. Autopsy disclosed pancreas of normal size except there was a tumor nodule, 1½ to 1 cm., located in the tail of the pancreas, and on microscopic examination diagnosed as a tumor of the island cells, probably carcinoma.

McClenahan and Norris[12] reported the third case. A colored male, aged forty-one years, had attacks of loss of memory, lasting from one to one and a half hours. They could be prevented by eating. Symptoms had been present six to eight months. Provisional diagnosis of encephalitis. Spinal fluid, 20 mg. sugar per 100 cc. spinal fluid; blood sugar, 40 mg. per 100 cc. blood. Patient died of

bronchial pneumonia forty-eight hours after admission to the hospital. Blood sugar remained low in spite of glucose intravenously. Autopsy revealed generalized arteriosclerosis. Examination of the brain showed cerebral irritation manifested in the form of slight perivascular round-cell accumulations. The pancreas showed a tumor, measuring 15 by 7 by 16 mm., located at the junction of the middle and distal thirds. Diagnosis: Adenoma of islands of the pancreas.

The fourth case was studied by Howland, Campbell, Maltby and Robinson:[13] In a case of dysinsulinism of six years' duration attacks of coma and convulsions, increasing in their frequency but warded off by the administration of food, were found to be caused by a low blood-sugar level. A study of the case revealed the erratic response to carbohydrate administration unless suitably administered and led to the diagnosis of this case as an islet-cell tumor of the pancreas. At operation a tumor of the pancreas was found and removed and a fruitless search for metastases was made. The patient recovered and has since been entirely free from the attacks. This constitutes the first successful treatment of such a case in the literature. The tumor was found to be a slow-growing carcinoma of the islet cells and insulin was recovered from the mass.

Warren[14] has recently brought together 20 such tumors observed postmortem.

With this brief review of hypoglycemia, the writer wishes to report the following case of hypoglycemia associated with a tumor of the left adrenal gland and congestion of the tail of the pancreas and pituitary body. So far as he can determine, it is the first case of hypoglycemia of its kind.

Case Report. A white male, aged thirty-three years, married, having a wife and two children, was admitted to the Conemaugh Valley Memorial Hospital in a semiconscious condition. He had influenza ten years ago. Three months ago he had multiple small abscesses over the scalp which have disappeared and returned in successive crops up to the present time. He had treatment of these with a salve which the family thinks contained some lead. He also had an infection of the jaw twelve years ago. He denies any history of venereal infection. The family history is not important. The patient felt well and taught school on April 24, 1929, and went to bed that night feeling well. The following morning he could not be aroused except to answer questions. He remained in this semiconscious state until 7 P.M., when he became thoroughly conscious and seemed normal, except he could not remember that he had been ill and thought it was morning and wanted to go to school. He remained normal for two days, until 2 A.M., April 26, when he again became semiconscious and slightly delirious and remained so until admitted to the hospital the same afternoon.

A few days before the patient began to have semiconscious states as noted above his wife states that he complained at times of visual disturbances. There was no diplopia but rather a dimness of vision at times. This was most apparent when he drove to school in the mornings. He also complained of not being able to see things clearly when he awoke the day before admission.

Physical Examination. A young man of apparently thirty years of age, well nourished and well developed, lies quietly in bed, although respirations are moderately increased. With the exception of many small furuncles and scars over the scalp, the skin is clear. The general color of the skin is slightly cyanotic. The skin is moist and superficial capillaries are dilated. The patient is in moderately deep coma, but can be aroused sufficiently so that he will move his arms and legs and mutter incoherently if the supra-orbital nerves are pressed upon. The pupils are equal and react to light. There is a definite nystagmus present. There is no paralysis of the oculo-motor nerves.

The teeth are in good repair; the tonsils are small; the throat is slightly congested but there is no acute inflammation. The ears are normal. There is no adenopathy. The thyroid gland is not appreciably enlarged.

The chest is well developed and normal to physical examination. The heart is normal in size and position and heart sounds are regular. Blood pressure was 120 systolic and 80 diastolic; pulse rate, 88; temperature, normal. The abdomen is negative, except for distention. The external genitalia are normal. Provisional diagnoses: Luetic meningitis, encephalitis, tuberculous meningitis, brain tumor, cerebral hemorrhage, brain abscess.

Clinical Course. Lumbar puncture produced clear fluid under normal pressure. At 6 P.M. respirations became irregular, pulse 120, with some rigidity of right arm. He was restless and perspired profusely. Chloral hydrate, sodium bromid and an enema were given. The following day he was still stuporous and restless and perspired profusely. In the afternoon 300 cc. of 20 per cent glucose solution was given intravenously. In half an hour the patient, aroused from his stupor, became conscious and took 6 ounces of orange juice with glucose. Later in the afternoon more orange juice and glucose were given.

On admission a Roentgen ray of the head was made and reported normal. The urine showed a heavy trace of albumin and a number of hyaline and granular casts, but nothing else of importance. The blood urea was normal. The spinal fluid was under normal pressure and presented a normal cell count and a negative Wassermann. An eye consultant stated that the fundi showed equal edema and venous congestion with chalky whiteness occupying the central position of each disk.

The patient rested quietly that night until 1 A.M. in the morning, when he became restless and semiconscious. During the early morning hours fruit juices were forced and he slept at intervals. He was clearer and quieter when morning came. Urine collected after intravenous glucose and fruit juices were given showed 10 per cent sugar. The blood count was 8000 leukocytes, 5,000,000 erythrocytes and showed a normal differential count. During the second and third hospital days the patient rested quietly and seemed improved, but at 2 A.M. in the morning of the fourth day he had a light convulsion and did not arouse from his sleep; but shortly afterward he became very restless and it became necessary to use a retention sheet. The body became rigid, the head retracted and he had an involuntary bowel movement. He sweated profusely and the lips and face became cyanotic. At 10 A.M. the patient was rigid, cyanotic, unconscious and sweating profusely. The pulse was irregular. A blood sugar showed 60 mg. per 100 cc. blood. Glucose by bowel was started and 300 cc. of 20 per glucose solution was given by vein. The patient's condition improved following glucose administration; but he remained semiconscious the remainder of the day and night. Eye consultant: "Retinal edema of right eye is greatly increased while left eye is much less. The chalky appearance is much greater of both disks and now resembles a complete nerve atrophy. The lesion is back of chiasm and to left central region." The

Wassermann and Kahn tests were negative and a second urine examination was reported normal.

On May 1, which was the patient's fifth hospital day, it became evident to the writer that, although the underlying disease process was obscure, the cause of this patient's symptoms was a hypoglycemia, and it further became evident that by giving sufficient glucose we could relieve these symptoms. So on the following days he was given an ample supply of carbohydrates. On several occasions in the early morning hours, when his carbohydrates ran low, he became restless and semiconscious and sweated profusely; but ample administration of glucose would relieve him.

Additional history on May 1 stated that four months previously, during a conversation at the home of one of his relatives, he paused in his conversation and was unable to talk for five minutes. Afterward he said he could think but could not express himself. About two weeks ago he had a short period in which he seemed to be irrational and said strange things. He has been rather listless and has had a tendency to become tired easily for six to eight weeks. It was also discovered that he saw double early in the present illness.

On May 3, his condition was much improved. He was rational, but thought came slowly. He had no headaches and no disturbance of vision.

The consulting neurologist reported: "When the man was first seen he was in deep stupor, not restless and free from motor excitement. There was a conjugated deviation to the left, but there seemed to be no (voluntary) eye muscle paralysis, as the eyes wandered about in all directions tending, however, to seek rest at the left. No pupillary irregularities. The mouth was drawn over to the right. Tongue movements not obtainable because of stupor. The eyegrounds appeared as follows: No edema; no papillitis; an ovoid area of shiny, glossy tissue at the region of the excavation, possibly an inflammation of the choroid more marked on the right. No evidence of increased intracranial tension.

The abdominal reflexes on the right were sluggish, on the left absent. Cremasterics normal. The limbs were all hypotonic. The reflexes in both upper extremities were normal. In the left leg there is a definitely positive Babinski, but a positive Gordon and Oppenheim. In both legs the patellar and Achilles reflexes are absent. It appears as if the man cannot voluntarily move any extremity; but the left arm and leg seem paralyzed, the right paretic. At the examination he could not be aroused from his stupor. He was incontinent. Sensation could not be tested on account of extreme stupor.

Today the picture has changed completely. The stupor is less marked; the man can be made to answer questions at times. There is singultus. The deviation of the eyes has disappeared, the facial paralysis has cleared up. The legs can be moved; the left Babinski is not elicited. (Oppenheim and Gordon still present.) There is obtained a history of slight personality changes two weeks ago. This recent psychosis, considered with the multiplicity of facial signs, and the fleeting nature of the signs, together with the objective findings enumerated above, lead to a diagnosis of subacute disseminated encephalitis.

On May 4 the patient is awake, talking and appears to be rational. He is rather restless, however, and his speech is slow and deliberate but not as marked as yesterday. He apparently has no visual disturbance. Stretches and sighs frequently as though he were very tired. No change in reflexes. Blood sugar, 157 mg. per 100 cc. of blood. On May 5 his condition was about the same, but he does not remember certain things that happened yesterday and did not remember certain visitors having been present. Eye examination shows fundi much clearer. Left eye has practically normal appearance except considerably central chalkiness of disk. Right eye vessels very tortuous with considerable hyperemia and chalkiness of disk.

FIG. 1.—The adrenal tumor with some normal adrenal tissue to the right. (×14.)

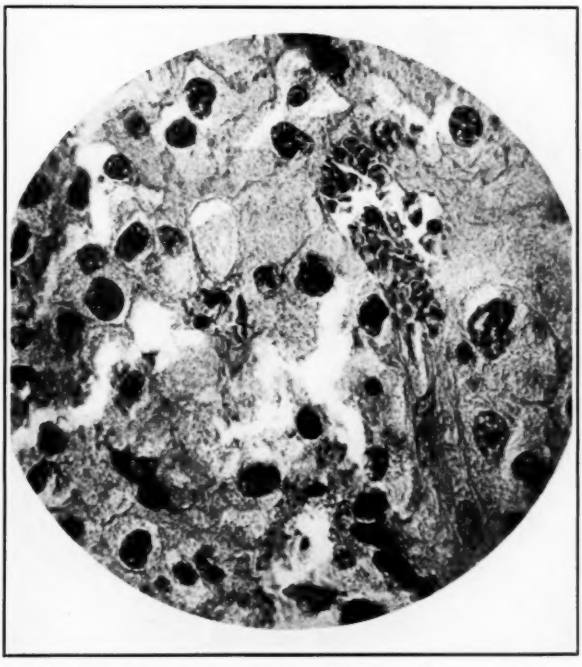

FIG. 2.—High power of the tumor, showing the general character and arrangement of cells. Note the relation to the capillary and the resemblance to adrenal cortical cells. (×627.)

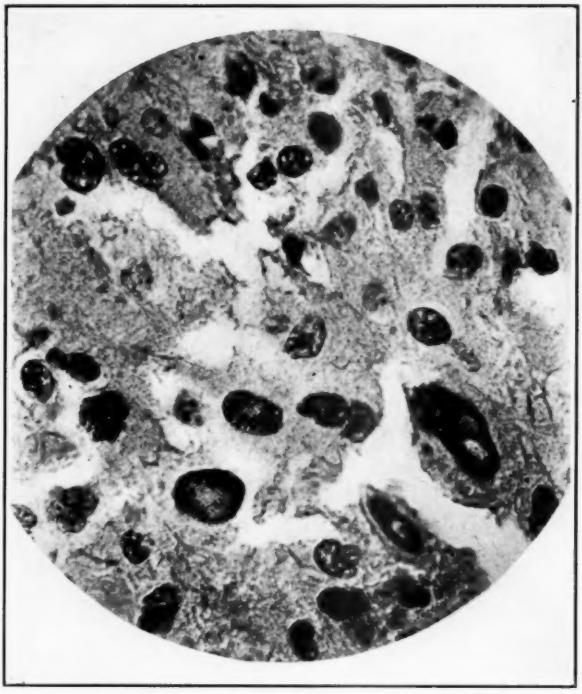

FIG. 3.—Another area showing the variations in size and the tendency to giant-cell formation. (×627.)

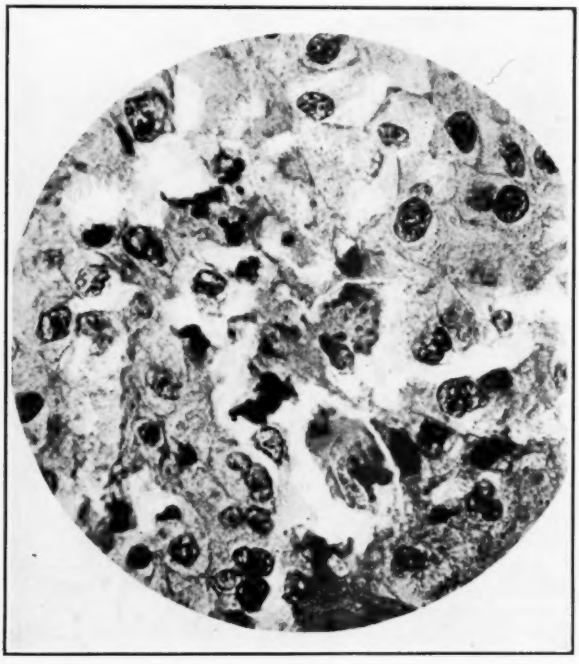

FIG. 4.—A rapidly growing area with tendency to cell degeneration. (× 627.)

The engorgement is about one-half as much as on April 30, 1929. On May 6 the patient offers no complaints, but states that he "feels fine." This state of euphoria was frequently noticed during his convalescence. The blood sugar was 150 mg. per 100 cc. blood at that time. On May 18, after steadily improving, he was allowed to go home. The family was instructed to give him plenty of carbohydrates, especially when there were signs of weakness, sweating or a disturbance of his mental state.

Second Admission. The patient was readmitted, July 3, 1929, in a state of coma. He had been normal in every way for about three weeks and a half, when he became violent and would strike any person in sight. A week later this attack cleared up after the family was able to administer glucose. Two days before admission he became stuporous at 2 A.M., but came out of it at 6 P.M. The day before admission he went into another attack which he was still in when he was admitted to the hospital.

On readmission it was evident that the patient had lost considerable weight while at home. He was in light coma and every few minutes he became quite restless. The eyes showed a nystagmus. The skin was very moist and of a dull and slightly ashen color. The superficial capillaries seemed dilated, and there was moderate cyanosis. Respirations were between 20 and 30, the pulse 120 and the temperature 102° F. The blood sugar was 69 mg. per 100 cc. blood. The urine showed a light cloud of albumin, but no casts. The blood count was 5,000,000 red cells and 8000 white cells. The spinal puncture presented a normal fluid under normal pressure. The blood pressure was 95 systolic and 80 diastolic. He was slightly improved at times during the next few days, but even though he was given glucose by mouth and bowel and intravenously, he gradually grew worse and died, July 8, 1929. During the last few days of his life he presented a typical picture of insulin shock. The pulse grew weaker and became rapid. The blood pressure fell to where it could not be taken. He was in a profuse perspiration constantly and cyanosis increased. He died with edema of the lungs. Adrenalin, in doses of 1 cc. of a $\frac{1}{1000}$ solution, was given several times during the last two days that he lived, but apparently it had no effect.

Blood-sugar determinations during the second admission ranged from 60 to 80 mg. per 100 cc. blood.

Autopsy. The body is that of a fairly well-nourished and well-developed man, thirty or thirty-five years of age. Except for a furuncle on the chin and two small pustules on the scalp, the skin appears normal. The brain and meninges were found normal. The bloodvessels were congested and there was slight edema. Gross and microscopic sections made through important centers of the brain showed no lesions. Bloodvessels constituting the circle of Willis were not sclerotic. Pituitary body was definitely congested, but otherwise normal. Abdomen: The peritoneum was moist, transparent and glistening and the diaphragm was normal in position. The liver extended to the lower costal border on the right. Its size, color and consistency were normal. The spleen was slightly enlarged, but the capsule was smooth and the cut surfaces uniformly reddish-brown in color. The left adrenal gland was the site of an encapsulated globular mass which measured 8 cm. in diameter and weighed 400 gm. The surfaces were reddish in color and very vascular. The capsule was thin, but at places remnants of adrenal tissue could be detected. There were several prominent bloodvessels in or immediately beneath the capsule. The tumor mass, although lying immediately on top of the left kidney, was in no way attached to it. The right adrenal gland was smaller and more fibrous than expected. The kidneys were normal. The pancreas showed a definite increase in vascularity, especially that portion constituting the tail. The stomach and intestines did not show any gross lesions.

The chest was not opened in the usual manner, but the diaphragm was

opened and the lungs examined. No metastatic growths were found nor were there any signs of pneumonia. The mediastinum was normal. The heart was normal in size and position. The valves were not examined. The autopsy findings may be summed up as follows: A tumor of the left adrenal gland and congestion of the pituitary and congestion of the pancreas.

The microscopic examination of the tumor was interesting. Dr. James Ewing, after examining a section of the tumor, stated that to him it looked more like a liver-cell tumor than an adrenal tumor; but being an adrenal tumor, he thought it must be a medullary and not cortical growth. A cortical growth ought to have destroyed the whole adrenal. However, he states the cortical adrenal growths have very large cells like those of this tumor.

Dr. Shields Warren, after examining the tumor tissue, gave the following expression: "The tumor appears to be a carcinoma of the cortex of the adrenal gland. This is a fairly rapidly growing tumor with numerous giant cells and multiple mitoses. A striking feature is the large vacuoles in the nuclei of the tumor cells which give me the impression that they originally contained glycogen. Certain tumors do contain very large amounts of glycogen and are also known to produce either insulin or a substance very similar to it. This substance produced by tumors goes by the name of insuloid in the literature on the subject. Certain of the experimental rat tumors are known to produce considerable amounts of insulin-like substance."

Dr. H. E. Robertson express the belief that the tumor was a carcinoma of the adrenal cortex. He further states, however, that as far as he knows, hypoglycemia has not been observed in cases with tumors of this kind heretofore.

Comment. While it may be admitted that hypoglycemia is either due to hyperfunction of the islet cells or to disturbed liver function, it must also be admitted that disturbances in the functions of other glands may be important contributory factors in causing a pathologically low blood sugar. The writer will not attempt to explain the relationship between the hypoglycemia and the adrenal tumor in the case just reported, but does feel that if all such cases are carefully studied and recorded, in time, a satisfactory explanation can be made. Another advantage in reporting all such cases is this: We read them and are more likely to think of them when we see such cases in our practice, and thinking of them leads us to the proper diagnosis. A prompt diagnosis and good surgery in such cases may save lives as it did in the case reported by Howland[13] and others. It is interesting to observe that in McClenahan and Norris'[12] case encephalitis was the provisional diagnosis; so it was in our case. They, however, found signs of perivascular round-cell infiltration in the brain which we did not find.

Summary. The case herein reported we feel is unique in that it is the only case we can find with typical symptoms of hypoglycemia

in which the only outstanding pathologic finding was a tumor of the left adrenal gland. There was also congestion of the pancreas and pituitary gland.

The symptoms were for a time relieved by glucose administration but later glucose failed to relieve the symptoms. Epinephrin was given one or two days before the patient died without effect. When the blood sugar fell below 0.07 the patient became restless, confused mentally and sweated profusely. The lowest blood sugar was 0.04 per cent.

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LIPOMA OF THE MEDIASTINUM.*

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Lipoma of the mediastinum is very rare. Only 11 cases could be found recorded in the literature. In only 1 case, that of Lemon, was the diagnosis made prior to operation or necropsy. In 3 of the cases the tumor was removed successfully at operation. The

* Presented to the Washington Society of Pathology.

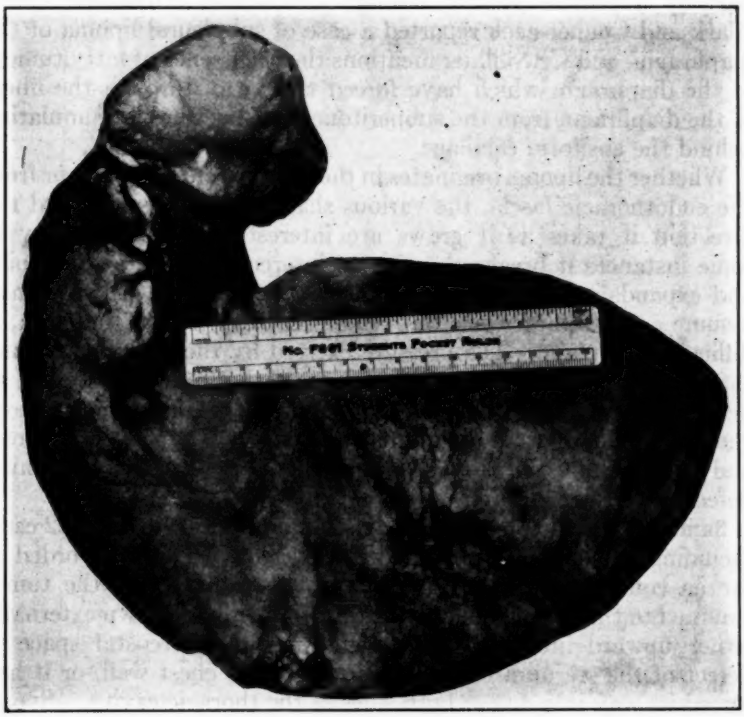
diagnosis was made in 2 instances after removal of a portion of the tumor which had forced its way through an intercostal space, and in another after removal of a small external tumor which was connected by a pedicle with the anterior mediastinum through a congenital aperture in the sternum. In the other 5 cases and in the 1 reported here the diagnosis was made at necropsy. The largest lipoma weighed 17 pounds and 6 ounces, and the smallest was about twice the size of a hen's egg. In 1 case the tumor was confined entirely to the anterior mediastinum. In 2 cases the tumor, relatively small, was situated in the superior mediastinum and projected into the neck, because of which location it was discovered in both instances. One or both pleural cavities contained part of the tumor in 6 cases. External tumors connected by pedicles with the internal lipoma through an intercostal space were present in 3 cases, and an external tumor connected by a pedicle with the internal tumor through a defect in the sternum in 1. In most instances the tumor was well encapsulated and easily shelled out. From the histologic examination only 2 of the tumors were diagnosed as congenital lipoma; the others which were examined were simple lipomas.

Well-marked symptoms due to pressure were noted in only 3 cases. Physical signs were recorded in 6. The accompanying table gives the salient data in the 11 cases previously reported and in the following case:

Case Report. A white man, aged forty-four years, entered Georgetown University Hospital on July 10, 1929, with the symptoms and signs of lobar pneumonia. He had had influenza in 1918 and claimed that ever since that time he had had some dyspnea on exertion. He had never missed a day at his vocation as a carpenter, and except for the mild dyspnea had been perfectly well. Two days before admission he had felt somewhat ill and soon developed a pain in the left lower chest anteriorly with cough and expectoration of a mucoid sputum which had become blood tinged. Examination on admission revealed a very robust man of good color, but evidently severely ill. He was groaning and dyspneic, with dilating alæ nasæ, and coughing rusty sputum. Crackling inspiratory râles were audible throughout both lungs, but there were no definite consolidations. There was flatness on percussion over the right lower chest with considerably diminished breath sounds. The cardiac sounds and blood pressure were normal. The abdomen was somewhat distended and tense, the tenseness being apparently due to enlargement of the liver. The temperature was 102° F., the pulse rate 100 and the respiratory rate 28. A Roentgen ray picture of the chest taken in bed with the portable machine revealed a dense opacity over the lower two-thirds of the right chest and an opacity also in the left chest corresponding to the lower part of the upper lobe. Examination of the sputum revealed pneumococcus Type IV. The hemoglobin was 79 per cent (Dare). The erythrocytes numbered 3,910,000 and the leukocytes 15,750 per c.mm. of blood, of which 87 per cent were polymorphonuclear neutrophils. The urinalysis showed a trace of albumin and a few leukocytes.

The patient's condition became progressively worse; the temperature rose to 105° F., the pulse to 146 and the respiratory rate to 30 a minute. Signs of involvement of the entire left lung developed. On the morning of the fourth day in the hospital the patient died.

Necropsy (Partial). On opening the thoracic cavity, a large light yellow tumor was seen to fill much of the right side of the thorax, the anterior mediastinum and to cover the pericardium. The mass was easily shelled out *en toto* and grossly appeared to be a lipoma. It was held in position by several layers of thin fascia and apparently originated from the fat in the superior mediastinum in the region of the thymus. The right lung was about one-third normal size and appeared normal. The entire left lung was completely consolidated and in the stage of red hepatization. The heart appeared normal but the pericardium was completely covered by a thick fold of the lipoma as before mentioned. The lipoma weighed $8\frac{1}{4}$ pounds, was relatively avascular and was nourished by two fairly large vessels. On section the tumor was seen to be a pure lipoma and was quite yellow (see illus.). Microscopic sections of the tumor showed that it was a pure lipoma.



Photograph of cut section of lipoma showing its lipomatous nature and its relative avascularity.

Comment. Lipoma of the mediastinum is not the only intrathoracic lipoma. A fatty tumor may also originate from the endothoracic fascia, from the subpleural fatty tissue of the diaphragm or from the subperitoneal fat forcing its way through the fibers of the diaphragm. Rokitansky noted that subpleural fat along the intercostal spaces is often abundant and at times projects into the pleural cavity as notable lobulated masses. Chiari is stated to have

observed in an elderly female a pendulous lipoma the size of a walnut projecting into the pleural cavity from the seventh left rib. Czerny removed a lipoma the size of a man's head from beneath the left scapula of a boy, aged eighteen years, which passed by a ramification into the extrapleural space between the seventh and eighth ribs. In his inaugural dissertation Plettner described in an elderly woman a lipoma the size of a child's head which projected from the left wall of the thorax and was found to connect with a flattened subpleural lipoma the size of a hen's egg by a pedicle between the fourth and fifth ribs. Gussenbauer's oft-quoted case was that of a lipoma at the border of the left mammary gland of a woman, aged twenty-nine years, which was connected to an intrathoracic counterpart by a pedicle passing through the second intercostal space. Clark and Conner each reported a case of subpleural lipoma of the diaphragm, and Cruveilhier mentions the occurrence of fatty tumors of the diaphragm which have forced their way through the fibers of the diaphragm from the subperitoneal fat, at times accumulating behind the ensiform cartilage.

Whether the lipoma originates in the anterior mediastinum or from the endothoracic fascia, the various shapes it may assume and the direction it takes as it grows are interesting features. Why in some instances it breaks through an intercostal space at one point and expands external to the thoracic cage, while in others it may assume a much larger size but remain entirely within the chest, is difficult to explain. The pressure exerted by the heart action and that produced by the lungs during inspiration may be assumed to be sufficient to cause part of the tumor to break through a congenitally weak spot in an intercostal space. The case of Garnier and Grosjean illustrates these factors in a patient with a congenital defect of the sternum.

Summary. Lipoma of the mediastinum is very rare, only 12 cases including the one described in this report having been recorded as far as could be ascertained. In only 1 instance was the tumor confined to the mediastinum. In the others it had grown externally either upward into the neck or through an intercostal space or defect of the sternum to form a tumor of the chest wall, or it had forced its way into one or both sides of the thoracic cavity. Symptoms due to pressure were noted in only 4 cases. In the case reported here moderate dyspnea on exertion had been present for eleven years, and the patient died of lobar pneumonia. The lipoma weighed 8¼ pounds and filled the anterior mediastinum, the precordium and the lower two-thirds of the right thoracic cavity.

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SALIENT DATA OF THE TWELVE CASES OF LIPOMA OF THE MEDIASTINUM.

Case.	Author.	Year.	Sex.	Age at death.	Location.	Size and shape.	Operation.	Cause of death.	Character of tumor.	Symptoms and signs.
1	Cruveilhier[1]	1856	?	?	Anterior mediastinum and externally by pedicle	?	Removal of external portion	Suppurative inflammation of anterior mediastinum	Pure lipoma	Details not given.
2	Krön'lein[2]	1887	F.	1 yr.	Anterior mediastinum, most of left and part of right chest; externally by pedicle through third right intercostal space	Internal part, size of child's head	Removal of external portion	Bronchopneumonia and pleuritis	Congenital lipoma	Few symptoms or signs.
3	Beatson	1899	M.	45 yrs.	Superior mediastinum and above sternal notch	Orange	Removed successfully	.....	Fatty lobules; no sections	No symptoms.
4	Garnier and Grosjean	1903	M.	56 yrs.	Anterior mediastinum and externally by pedicle through defect in sternum	External part walnut size	Removal of external portion	.....	Pure lipoma	External tumor and pain for three months.
5	Fitz	1905	M.	34 yrs.	Anterior mediastinum and left thoracic cavity	Pear shaped; size of fetal head	None	Purulent pericarditis	Congenital because of hypoplasia of left lung	No symptoms; physical signs of tumor.
6	Ewing	1905	M.	Middle age	Anterior mediastinum, lower half of left chest, ramifying in many directions	Five main lobules, each size of goose egg	None	Pneumonia of right lung	Lobules connected by broad pedicles; fetal fat tissue	Dissecting room cadaver; no history.
7	Bertoli	1908	M.	57 yrs.	Left side of anterior mediastinum	Covered 8 sq. cm.	None	Empyema of right side	Lobules (12), numerous capillary sinuses and scattered monocytes	No symptoms recorded.
8	Leopold	1920	M.	37 yrs.	Anterior mediastinum, right and left thoracic cavities	17 pounds, 6 ounces	None	Asphyxia	Large fat cells	Cough and dyspnea, 17 mos; edema from below upward, 9 mos.; cyanosis of head and arms.
9	Beyers	1923	M.	22 mos.	Anterior mediastinum and externally by pedicle through sixth left intercostal space	Each portion about 2 in. in diameter	Removed successfully	.....	Pure lipoma; section not reported	No symptoms; external tumor noted for 12 mos.
10	Lemon	1925	M.	48 yrs.	Anterior mediastinum and right thoracic cavity	Size of quart cup	None	Asphyxia	Pure lipoma; lobulated	Pressure symptoms, 7 yrs.; cough, hemoptysis, dyspnea, cyanosis; physical signs of tumor.
11	Graham and Wiese	1928	M.	43 yrs.	Anterior mediastinum and suprasternal	Twice size of hen's egg	Removed successfully	.....	Pure lipoma	Choking spells, 6 mos.; pain in neck and right chest; cyanosis of finger tips at times; numbness of right arms and chest at times.
12	Yater and Lyddane	1929	M.	44 yrs.	Anterior mediastinum, precordium and lower two-thirds of right thoracic cavity	8¼ pounds	None	Lobar pneumonia, entire left lung	Pure lipoma	Mild dyspnea, 11 yrs.

[1] Case of Morel-Lavallée.

[2] Reported by Vogt, 1876.

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ALIMENTARY HYPERLIPEMIA.

A Study of the Lipemic Curve.

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Under normal conditions the amount of fats in the blood stream maintains a constant level and only during the postprandial period does it rise temporarily. It is interesting for the clinician to study the changes in this curve during alimentary hyperlipemia and its variations under abnormal conditions. It is more than probable that such a study may throw some light on the thus far unsolved problems pertaining to fat metabolism and it may even prove to be useful as a clinical method of investigation.

The technique for the determination of fats in the blood stream is complicated, a fact which no doubt has been the reason why thus far this method of investigation has not been widely used. Four years ago Vanysek studied this problem in our clinic. At that time we tried to determine the fat content by the use of Bang's method and determined the petroleum content of fatty acid and

cholesterin, but our results were not satisfactory; there remained to try other macromethods which in themselves were accurate, but were not available to us because of their great complexity and the impracticability of making serial observations. Bloor's method was finally chosen for our purpose.

I am, therefore, continuing the investigations for Vanysek,[1] who has reviewed the literature of fat metabolism in the human body.

That which we summarize under the general conception of lipemia is really a summary of metabolites which vary widely both chemically and physiologically and yet maintain their quantitative interrelationship (Terroin's *constance lipémique*). For example, if we burden the organism with neutral fats there is an increase in the blood content not only of the neutral fats but also of cholesterin. The other fatty bodies behave similarly. All the fats which are taken in as food lipoids are also present. Moreover we know that cholesterin is absorbed when it has been administered together with neutral fats, whereas pure cholesterin will pass out with the feces. It seems, therefore, that in the study of fat metabolism it is correct first of all to study lipemia.

Under normal conditions the fasting fat level, as determined by the method of Bloor, lies between 0.5 and 0.7 per cent. The fat is present in the blood stream as a fine emulsion. Under normal conditions the serum is clear and only when the fat content reaches above 1 per cent (according to Bloor) does the hyperlipemia appear as a milky discoloration. The only exception is the so-called masked hyperlipemia which accompanies the so-called retention icterus (Brulé), in which in spite of a high hyperlipemia the serum is clear; the cause for this is apparently the concentration in a fine state of emulsion.

After the ingestion of fat one can follow the course of hyperlipemia microscopically by the appearance of milky serum and, finally, by its disappearance (hemoconia). In the literature one finds that the fat level starts rising two hours or more after the absorption of ingested fat reaches the blood stream through the chylous channels and through the thoracic duct. Such a hyperlipemia reaches its highest point in about six hours and in from eight to ten hours the lipemia returns to its normal level. Bang has shown, however, that if we use smaller doses (from 20 to 50 gm. of butter) the curve is markedly shortened and reaches its maximum in three hours.

In this work, therefore, I have used as a test breakfast 50 gm. of butter given with one roll of bread and 0.25 liter of slightly sweetened coffee with cream. The lipemia estimations were made at intervals of one and a half hours. I found that under normal conditions the fat level at the end of one and a half hours was not changed, in three hours it was slightly raised, in four and a half hours the curve reached its maximum level and in six hours it returned to its original

value. The ratio of the maximum lipemia to the fasting lipemia averaged about 1.3. From these experiments we secured a certain type of curve which we could consider as normal in type and other curves that could be considered as pathologic variations.

Nineteen cases in which lipemia estimations have been made are summarized in Tables I to III and the lipemia curves in these cases are shown in the charts.

TABLE I.—NORMAL RELATION OF FASTING TO MAXIMUM LIPEMIA.

Case No.	Age.	Diagnosis.	Fasting lipemia, per cent.	Lipemia (per cent) after ingestion of fat.					Ratio of fasting to maximum lipemia.
				1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	7½ hrs.	
1	52	Mesaortitis luetica; aortic aneurysm	0.56	0.56	0.65	0.73	0.56	...	1.30
2	16	Acute anterior poliomyelitis	0.66	...	0.81	0.86	0.66	...	1.30
3	32	Trauma of spine; paraparesis of lower extremities	0.73	0.73	0.77	0.96	0.73	0.73	1.31
4	44	Traumatic neurosis	0.60	...	0.65	0.81	0.60	...	1.35
5	18	Muscular atrophy	0.42	...	0.48	0.54	0.42	...	1.29
6	51	Gastritis; hypoacidity	0.54	...	0.58	0.69	0.54	...	1.28
7	27	Sine morbo	0.56	...	...	0.73	0.56	...	1.30

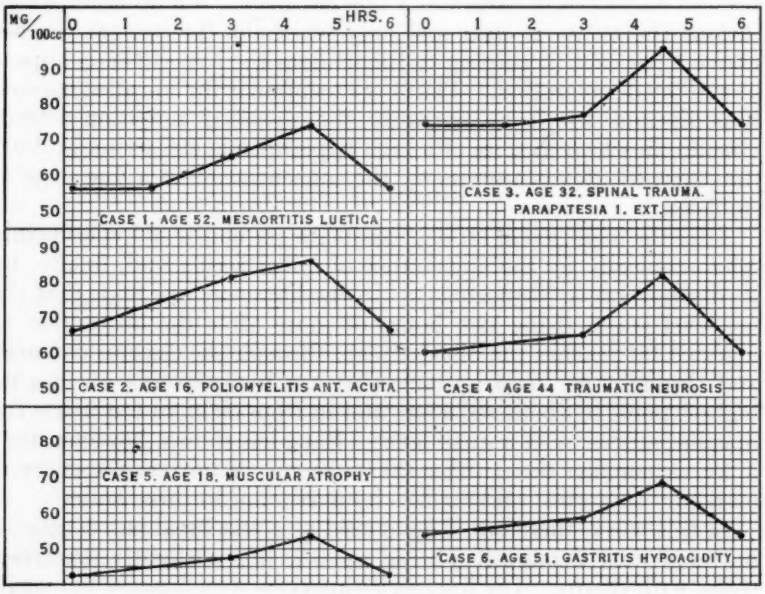
MG/100cc
HRS.
CASE 1, AGE 52. MESAORTITIS LUETICA
CASE 3. AGE 32. SPINAL TRAUMA. PARAPATESIA 1. EXT.
CASE 2. AGE 16. POLIOMYELITIS ANT. ACUTA
CASE 4 AGE 44 TRAUMATIC NEUROSIS
CASE 5. AGE 18. MUSCULAR ATROPHY
CASE 6. AGE 51. GASTRITIS HYPOACIDITY

CHART I.

From the findings given in these tables we may conclude that only the first 7 (Table I) had a normal lipemia (the muscular-atrophy case alone has a markedly low-fasting lipemia). As was stated above,

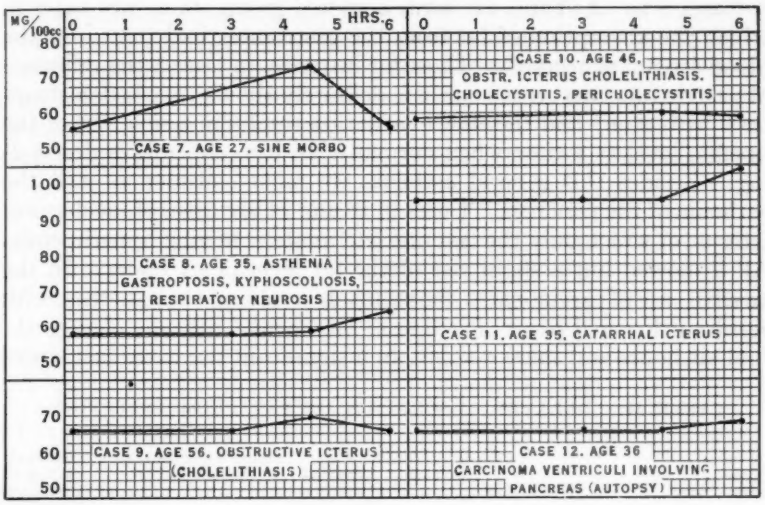

CHART II.

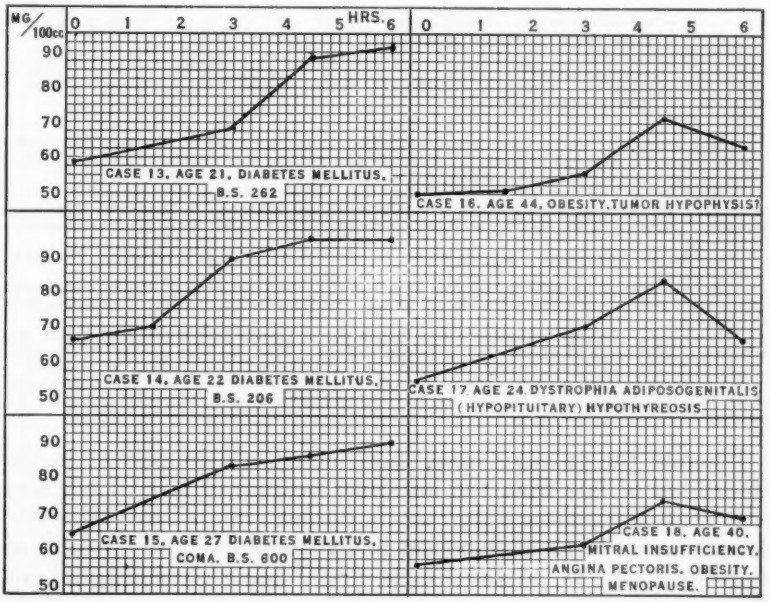

CHART III.

the hyperlipemia appears between the second and third hour after the ingestion of fat and reaches the maximum between the fourth and fifth hours, returning to its original value during the sixth hour. The normal lipemic ratio is between 1.27 and 1.35.

Cases 8 to 12 (Table II) form a second group; these are cases in which the absorption of fat from the gastrointestinal tract into the blood stream is delayed. Thus, for instance, in Case 8 the influence of gastric function on the curve is definitely shown; marked gastroptosis with atony and the slow evacuation results in a slow rise of the lipemia level at a time when normally the hyperlipemia is descending. Besides this general asthenia we must consider as well the asthenia of the pancreas. Cases 9, 10 and 11 are cases of mechanical icterus, of which only the last one had a latent fasting hyperlipemia. All 3 showed but a slight rise of the fat level in six hours. In the twelfth case of carcinoma of the stomach involving the pancreas, with resultant lowered pancreatic lipase, the lipemia did not change the first six hours and there was but an insignificant rise in the last hours.

TABLE II.—DELAYED ABSORPTION OF FAT FROM INTESTINE.

Case No.	Age.	Diagnosis.	Fasting lipemia, per cent.	Lipemia (per cent) after ingestion of fat.			Ratio of fasting to maximum lipemia.
				3 hrs.	4½ hrs.	6 hrs.	
8	35	Asthenia; gastroptosis; kyphoscoliosis; respiratory neurosis[1]	0.58	0.58	0.59	0.65	1.12
9	56	Obstructive icterus (cholelithiasis)[2]	0.66	0.66	0.69	0.66	1.05
10	46	Obstructive icterus (cholelithiasis); cholecystitis; purulent pericholecystitis[3]	0.58	...	0.60	0.59	1.03
11	35	Catarrhal icterus[4]	0.95	0.95	0.95	1.04	1.09
12	36	Carcinoma ventriculi involving pancreas (autopsy)[5]	0.66	0.66	0.66	0.68	1.03

[1] The Roentgen ray in this case showed a markedly elongated stomach, reaching five fingers' breadth below the left crest of ilium; it was atonic and emptied very slowly. The urine showed traces of sugar several times. Glycemia, 102 mg. per 100 cc. of blood.

[2] Icterus lasting two months, serum bilirubin, 16. Glycemic curve, after glucose and after levulose of the liver type. Duodenal secretion contained bilirubin, 5; ferments: trypsin, 7; diastase, 7; lipase, 8 units. Gastric analysis: Free hydrochloric acid, 40 per cent; total acidity, 75 per cent.

[3] Purulent pericholecystitis. Acholic stool. Duodenal secretion had no bilirubin. Ferments, 10 per cent.

[4] Catarrhal icterus. Icterus lasted over three months. Serum bilirubin, 5 units (one month before when patient was admitted it was 20 units). Stool somewhat colored. Urine contained no bilirubin.

[5] Roentgen ray findings: Carcinomatous narrowing of prepyloric portion of stomach, carcinomatous infiltration of gastric wall. Gastric analysis: Free and total acidity, 0; ferments, 15 per cent. Occult blood present in stool. Duodenal secretion: Trypsin, 9; diastase, 9; lipase, 4; blood diastase, 3 units. Glycemic curve after glucose showed blood sugar amounting to 50, 150, 250, 338, 274 and 182 mg. per 100 cc.; with glycosuria at the end of first hour, 0.8 per cent.

Whereas the previous cases show merely a derangement in the absorption of fats from the intestines because of lack of bile and of the pancreatic lipases, the cases in the last group (Table III) show derangements of fat metabolism in the tissues. In the 3 cases of diabetes (Cases 13, 14 and 15) the first 2 had a glycemia of about 200 mg. per 100 cc. and no acidosis with a normal lipemia; the third case entered with a severe acidosis, with a glycemia of 600 mg. per 100 cc., lipemia 1.3 per cent and an alkali reserve of 12 per cent. After fourteen days of intensive treatment with insulin the glycemia fell to 400 and the lipemia to 0.64 per cent. In all 3 of these cases the lipemic curve differed from the normal curve, the lipemia rose earlier, reached higher values, and the quotient ratio was 1.4 to 1.58

and even after six hours still had a tendency to rise. In diabetes the lipemic curve appears to be quite analogous to the glycemic curve, and this analogy demonstrates the relation between the fat metabolism and the carbohydrate metabolism. During the course of lipemic curves in cases of obesity (Cases 16 and 18) and in dystrophy adiposogenitalis (Case 17) we can note an analogy to the

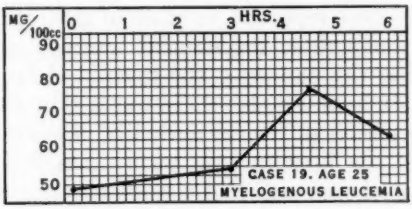

CHART IV.

prediabetic curve in obesity which is also found in Case 16, in which there is a high quotient and a prolongation of the downward curve. On the other hand, in the last case of myelogenous leukemia (Case 19) there is a similar curve. How far the spleen or reticuloendothelial system plays a rôle here, we are not in a position to say.

TABLE III.—ABNORMAL ABSORPTION OF FAT FROM INTESTINE.

Case No.	Age.	Diagnosis.	Fasting lipemia, per cent.	Lipemia (per cent) after ingestion of fat.				Ratio of fasting to maximum lipemia.
				1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	
13	21	Diabetes mellitus (glycemia, 262 mg. per 100 cc.; glycosuria, 1.2 per cent; no acetonuria)	0.58	...	0.68	0.89	0.92	1.58
14	22	Diabetes mellitus (glycemia, 206 mg. per 100 cc.; no glycosuria, acetone or acetoacetic acid)	0.67	0.70	0.89	0.95	0.95	1.41
15	27	Diabetes mellitus[1]	0.64	...	0.83	0.86	0.90	1.40
16	44	Obesity; hypophyseal tumor[2]	0.50	0.51	0.56	0.72	0.63	1.44
17	24	Dystrophy adiposogenitalis (hypopituitary); hypothyreosis[2,3]	0.55	...	0.70	0.83	0.67	1.51
18	40	Mitral insufficiency; angina pectoris; obesity; menopause; wt., 95.4 kg.	0.56	...	0.62	0.74	0.69	1.32
19	25	Myelogenous leukemia[4]	0.48	...	0.54	0.77	0.63	1.60

[1] Entered in coma; glycemia, 500 mg. per 100 cc.; acetonuria, 2+; acetoacetic acid, +; alkali reserve, 12; lipemia, 1.3 per cent. Fourteen days after entrance, on the day of experiment, glycemia was 400 mg. per 100 cc. and glycosuria 1 per cent; there was no acetone. This patient received daily over 100 units of insulin.

[2] From 1917 to 1919 the patient's weight increased from 70 to 125 kg. Since then the weight had been around 120 kg. (264 pounds). The nasal aperture continuously expanded; the skin was getting rougher; headaches occurred. Eyesight and smell were normal. Glycemic curve after 50 gm. glucose showed blood sugar amounting to 130, 190, 210 and 158 mg. per 100 cc. Urine sugar, +, but − two hours later. Basal metabolism, −11 per cent. Specific dynamic action of protein after ingestion of 170 gm. of ham raised the basal metabolic rate 30 per cent. Roentgen ray showed irregular enlargement of the sella turcica.

[3] Since childhood the patient had been small and fat; studied well. Menstrual periods started at age of eighteen, none since then. Had frequent headaches. Urination normal. Weight, 59.6 kg. Roentgen ray showed a total ossification of sella turcica. Vision normal. Liquids were excreted in a normal fashion; urine concentration normal. Specific dynamic action of protein after ingestion of 200 gm. of ham raised basal metabolic rate from −16.5 per cent to +5 per cent in sixty minutes.

[4] The spleen filled nearly the entire abdomen and reached clear to the crest of ilium distally between the umbilicus and symphysis pubis, on the right to the midclavicular line.

This report was not meant to go any further into the theoretical considerations as much more work will be necessary before we can come to any definite conclusions.

Summary. 1. In a normal individual hyperlipemia appears between the second and third hours after the ingestion of fat, and reaches its maximum between the fourth and fifth hours, returning to its original value during the sixth hour.

2. In the series here reported, in cases of gastroptosis with atony, asthenia of the pancreas, mechanical icterus, carcinoma of the stomach involving the pancreas, the lipemia either did not change during the first six hours or else there was a slow rise of the lipemia level during the period in which, normally, lipemia is decreasing.

3. In diabetes the lipemia rose earlier, reached a higher level, and even after six hours still had a tendency to rise. The lipemic curve in diabetes appears to be quite analogous to the glycemic curve. This analogy demonstrates the relation between the fat metabolism and the carbohydrate metabolism.

4. In obesity and in adiposogenitalis and dystrophy, myelogenous leukemia, the leukemic curve is analogous to the prediabetic curve.

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ATROPHY OF SUBCUTANEOUS FAT ASSOCIATED WITH INSULIN INJECTIONS.*

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During the past three or four years there have appeared in medical literature a number of reports of cases of atrophy of the subcutaneous fatty tissue at or near localities in which insulin injections have been made over considerable periods of time. The condition is illustrated by a case which has come under my observation, the particulars of which are as follows:

Case Report. The patient, a widow, had lived an active life, and been subjected to much strain. She had had 2 children—a daughter, dying of diabetes at the age of twenty-two years, and a son, now living at the age of thirty years, also a diabetic. Her weight at the age of twenty-five years was 165 pounds; height, 64 inches. At the age of forty-four years she had a vaginal operation for uterine fibroids, with no subsequent hemorrhage; Roentgen ray at present shows an opaque rounded mass in the pelvis, apparently a calcified fibroid. A benign tumor was removed from her left breast at the age of forty-nine years.

In 1924, at the age of fifty-five years, she was discovered to have diabetes, with urinary sugar, 7.9 per cent; and fasting blood sugar, 340 mg. in 100 cc.; there was also some nephritis, with hypertension (to 220 systolic), and

*Read before the Medical Society of the District of Columbia, March 19, 1930.

cardiac arrhythmia; weight, 102 pounds; chief complaint, asthenia. Dietetic and insulin treatment was instituted in September, 1924, and kept up faithfully for a few months, with satisfactory improvement. The nephritis and hypertension largely subsided. Her weight in April, 1925, had increased to 134 pounds.

During the next four years the insulin injections, 20 to 30 units daily, were continued, but the dietary regimen was faulty.

During the winter of 1926–1927 she discovered that there was a complete disappearance of the subcutaneous fat over her lower abdomen, involving in general a circular or oval area from the navel to the pubes. There were also several similar atrophic depressions or hollows "bigger than hickory nuts" in the anterointernal aspects of both thighs. The insulin injections had been administered in the outer part of the lower third of both thighs, several inches below the atrophic areas; and in the outer iliac regions of the abdominal wall on both sides, external to the location of the suprapubic atrophic area. The disappearance of the fat had been entirely unaccompanied by any pain or other symptoms. The injections were made aseptically, and no infection had occurred. The patient's weight at this time was 100 pounds. She subsequently changed the site of the injections to the arms.

In May, 1929, the patient again came under my observation, complaining especially of insomnia, severe nocturnal pains in the back and trunk, marked constipation and dysuria. There was some ataxia of station and gait and enfeeblement of the reflexes; diabetic myeloneuritis or pseudotabes was diagnosticated by a neurologist. Her weight was 125 pounds; there was hyperglycemia and high urinary sugar; Wassermann and Kahn reactions negative; other conditions negative or irrelevant.

In the suprapubic region of the lower abdomen there was a considerable area, as large as the palm of the hand, where the subcutaneous fat was completely atrophied and absent, and the thinned fatless cutis lay directly on the abdominal fascia and muscles, over which it was very freely movable, and the markings of which were plainly palpable and almost visible. This atrophic area extended below to the pubes; above it was bounded by irregular abrupt and thick rounded edges of the subcutaneous fatty tissue extending downward in several projections into the atrophic region. The area of atrophy was stated to have originally extended to the navel; but over the upper half the adipose tissue had regenerated and was growing downward by several projecting masses of full thickness and with abrupt rounded edges or promontories into and gradually filling up the depressed area. The defect was being replaced not by general deposition of new fatty tissue over the entire defective area, but by growth and advance of the panniculus adiposus in its entire thickness from above downward. Although the disappearance of the fat in the first place had been unattended with any pain or sensation, the regeneration of the masses of fat was accompanied by severe and constant local pain and soreness, of which the patient bitterly complained.

In the anterointernal regions of both thighs there were several rounded depressions formed by similar defects of the underlying fat. These had originally been much larger; but regeneration of the adipose tissue had been in progress and lessened their size.

The subsequent course of the case has no bearing on the adipose atrophy. The diabetic conditions were improved; but the psychoneurotic history for a time was stormy.

At the present time (December, 1929), seven months later, the regeneration of the fat has progressed markedly. The depressions in the thighs have almost disappeared. The large suprapubic defect has been filled with new adipose tissue over its entire base; but the surface still shows a number

of deep, rounded depressions, giving an irregular undulating contour to the skin. The pain formerly associated with the regeneration of the fat has entirely ceased.

The earliest report of local fat atrophy following insulin injections appears to have been one of 5 cases by Depisch, in October, 1926; Barborka, of the Mayo Clinic, independently observed and reported 2 cases in November, 1926. In 1927 2 cases were reported by Davison, and Mentzer and duBray; in 1928, 17 cases, by Carmichael and Graham, Chapman, Rabinowitch, Preisel and Wagner and Awrounin (Avery); and in 1929 I have found a report of 8 cases in children by Fischer; a total, including my report, of 35 cases. A special collection and review of the data of 21 of the cases was presented by Avery in 1929.

It is probable that the condition, if borne in mind and looked for, would be found to occur more frequently than the paucity of the cases heretofore reported would indicate; since Depisch alone saw 5 cases, and Rabinowitch found 8 cases in the metabolism clinic of the Montreal General Hospital. Fischer, among 24 children who had been receiving insulin injections for more than six months, found 8 marked cases of the atrophy, and 8 slight cases; while only 2 out of 15 children failed to show some atrophy after more than one year of insulin treatment. Similar statistics for adults have not yet been presented.

The lesions consist of areas of atrophy and disappearance of the subcutaneous fat at or near the sites where hypodermic insulin injections have been administered over a considerable period of time. They therefore usually occur on the thighs or arms; or over the abdomen, as in my case. In the most marked cases, there are large areas, sometimes reaching the size of the palm of the hand, where the panniculus adiposus is completely absent and the thinned fatless cutis lies directly on the underlying muscular and facial structures, which are distinctly and startlingly palpable, and even almost visible. The less extreme or moderate cases consist of oval or oblong depressed areas of the skin, or rounded depressions like large dimples. In the slightest perceptible traces of the condition there is merely a slight flattening of the skin with a little thinning of the panniculus, more evident to palpation than to sight. The cutis is probably ordinarily unchanged, and freely movable over the underlying fascia; although induration of the skin has been noted, and also adhesion to the underlying structures.

The atrophic areas are not necessarily situated at the exact sites of the injections, but may be located at a little distance in their neighborhood, perhaps in the course of the lymphatic drainage away from the injections. There are frequently several of the lesions present in each affected individual.

The development of the atrophy is unattended with pain or other subjective symptoms; there is no indication of any inflammatory

process, nor of any neural participation or etiology in the changes. The condition may not be noticed until after it is fully developed. The process is apparently exclusively an atrophy of the fatty cells or adipose tissue, and no other tissues or cells are involved. In the case of Mentzer and duBray "sections taken from the depressed areas showed no lymphocytic foci indicative of inflammatory changes;" in this case a small calcified nodule a centimeter in diameter was situated contiguous to the depression.

In the reported cases the duration of insulin injections prior to the appearance of the atrophy has ranged from three months to three and a half years. The antecedent duration of the diabetes has varied from six months to eighteen years. The dose of insulin has been from 10 to 120 units daily, injected from one to three times a day. It is noted in several of the cases that although insulin was taken, the dietary regimen was faulty. Body build has no bearing on the development of the lesions, as some of the patients have been obese, others slender. The duration of the period of development of the atrophies, from their first inception to the attainment of full size, is not indicated in the reports.

As to sex, so far as stated, 7 cases occurred in males, 16 in females; apparently indicating somewhat greater susceptibility of females.

All ages are susceptible. Fifteen of the reported cases occurred in children, in the first and second decades; the details of the ages and sex are not stated. Possibly children, with their more delicate tissues, are more subject to the atrophy than are adults; this perhaps also explains the greater susceptibility of females. Of 20 cases in adults, 2 occurred at the ages of twenty to twenty-nine years; 6 from thirty to thirty-nine; 4 from forty to forty-nine; 7 from fifty to fifty-nine; 1 at sixty.

In only 2 of the cases is regeneration of the atrophied tissues noted, the other case reports not having covered sufficiently long periods of observation. In Chapman's case, insulin had not been used for two and a half years, and the affected thigh had returned to normal. In my case, over a period of three years there has been extensive regeneration, although not yet complete; in this case the regeneration was attended with severe local pain and soreness (perhaps comparable with that of adiposis dolorosa). From these two cases it appears probable that after cessation of the injections complete regeneration from extensive atrophy may be expected in the course of two to four years.

Various explanations of the causation of the atrophic process have been considered, but no final conclusion has been reached.

That it is a result of the diabetic condition *per se* is unlikely. Diabetes, it is true, involves a disturbance of fat metabolism, but that is of a biochemic nature general in its operation, and not a local histolysis. No cases have been reported in diabetes except in conjunction with the use of insulin.

Antiseptics used for sterilization can be eliminated as causative, since various methods of disinfection were used in the cases—alcohol, cresol, lysol, boiling. Infections have not been responsible. Faulty technique of the injections has been blamed, especially their limitation to a too restricted area; but this can be only a secondary factor. Contamination or peculiarities of the make of insulin employed can be excluded, since the insulin used in the reported cases came from several different sources.

It is natural to suspect the local action of the insulin itself as the specific cause of the fatty atrophy. Insulin is a pancreatic product. One of the active properties of the pancreatic secretion is lipolysis. Fatty necrosis is one of the results of pancreatic disease. Lipase is not, however, supposed to be present in the commercial preparations of insulin; and Rabinowitch was unable to detect its presence in concentrated preparations. This does not exclude the possibility that a precursor of the enzyme is present, which in contact with the body fluids becomes activated and exerts lipolytic properties.

It is well known that the oxidation of fat in the body is largely effected by the oxidation of the carbohydrate; as it is frequently expressed, fat burns in the flame of carbohydrate. My own suggestion as to the causation of the fatty atrophy in these cases is this: that the strong initial concentration of insulin in the subcutaneous tissues near the site of injection causes an active local oxidation of carbohydrate, which in turn causes an active combustion of the local fat.

Another causative possibility is open for consideration. Is the atrophy due to long-continued frequently repeated traumata or other effects involved in the hypodermic injections as such, independently of the insulin? Data for adquate comparison are lacking, since in no other common conditions is hypodermic medication so prolonged and intensive as in diabetes. However, Mentzer and duBray state that in narcotic addicts they have observed several instances of atrophy of subcutaneous fat; microscopic examination of these lesions invariably showed foci of lymphocytes and polymorphonuclear leukocytes, indicating an inflammatory condition different from the apparently purely atrophic process of the insulin lesions.

Avery considers the lipodystrophy from insulin as a "traumatic atrophic panniculitis," due to the repeated hypodermic traumata. He bases his theory on 2 cases of definitely inflammatory panniculitis, with atrophy, which he cites; these cases were, however, entirely different in character from insulin atrophies, and would not seem to have any bearing on the pathology of the latter.

Lawrence reported results of microscopic examinations of skin from areas where many insulin injections had been made (not from patients with fatty atrophy); he found only a tendency to slight fibrosis and increase of connective-tissue cells in the subcutaneous fat.

Bowie and Robinson on examination of sections from the infiltrated areas of the skin of rabbits soon after insulin injections were made found only, aside from the wide separation of the cells, degenerative changes in some of the superficial muscle fibers; but similar changes occurred after injection of other solutions not containing insulin.

In the way of treatment, it is obvious that injections in the vicinity of the affected areas should be discontinued. As a preventive measure, the sites of the injections should not be confined to limited areas, but should be occasionally changed and well distributed.

Summary. Prolonged hypodermic administration of insulin sometimes causes atrophy of the subcutaneous fatty tissues in the vicinity of the injections. In this paper a case of the kind is reported and 34 other cases in the literature are reviewed.

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A CLINICAL STUDY OF ONE HUNDRED AND THREE CASES OF SCLERODERMA.*

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Scleroderma is chronic dermatosis characterized by diffuse or localized induration, pigmentation and sclerosis of the skin. The manifestation varies from small single patches to involvement of the entire tegument; hence it is divided into two types, the diffuse or generalized, and the localized.

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The diffuse form of scleroderma (Fig. 1) may begin with symptoms of arthralgia, malaise, loss of weight and asthenia, or with vasomotor phenomena in the extremities similar to the type found in Raynaud's disease. The course of the disease varies as to the extent and degree of involvement; it may remain stationary for years, and rarely it may disappear without sequelæ. Numerous cases have been observed in which the induration disappeared, leaving profound atrophy of the skin, but more frequently there is slow but continuous progression of the disease until death results.

Circumscribed scleroderma includes the three varieties of the disease known as morphea (Fig. 2), scleroderma in bands (Fig. 3), and guttate scleroderma. The circumscribed type most commonly begins as a single, rarely several, and more rarely as many white, pink, or slightly congested patches. These patches spread peripherally, showing a lilac-colored border, while in the center of the plaque, pigmented or whitened atrophic patches develop. Occasionally in the early phase of the circumscribed form, the elevated, ivory-yellow indurated characteristic patches of the diffuse form of scleroderma may be seen.

In the data considered here, 103 cases were studied. There were 48 cases of generalized scleroderma and 55 cases of the various forms of circumscribed scleroderma.

Generalized or Diffuse Scleroderma. It is essential to know the features that characterize the onset of the generalized type of scleroderma, because during this phase of the process other diseases may be simulated. There are two common types of symptoms in the beginning. Pain, swelling and stiffness of the joints, usually of the hands, but often diffuse and accompanied by systemic symptoms, were found in 58 per cent of the cases of generalized scleroderma. Vasomotor symptoms in the extremities, of varying severity, were found in 33 per cent. In only 8 per cent was none of these symptoms present at the beginning. These data are at variance with the general conception of the disease, which is that the onset is unaccompanied with premonitory symptoms.

Symptoms. Osler,[28] in 1898, reported in detail 8 cases of scleroderma. In 5 of these there were symptoms of an arthritic nature which varied from generalized recurrent arthritis to swelling and stiffness of the hands. In one case there was vasomotor disturbance of the hands and feet strongly suggestive of Raynaud's disease. The occurrence of acrocyanosis, acroasphyxia and other symptoms suggestive of Raynaud's disease has been noted by many writers. Vasomotor disturbances of the extremities was less common than arthritic symptoms in our series, but such disturbances seem to have attracted more attention in the literature. Among writers who specifically have emphasized these vasomotor phenomena are Hutchinson, Castle, Favier, Thiebierge and Weissenbach, Scholefield and Weber, Alquier and Touchard, and Longcope.

In the group of 48 cases of generalized scleroderma, 28 (58 per cent) presented arthritic symptoms as the earliest manifestation of the disease. The extent and severity of the symptoms in the joints were extremely variable. The milder cases evidenced only a little pain, swelling and stiffness in the hands, followed by hardening of the skin, whereas in the extreme cases there was generalized severe pain of joints and muscles, with swelling and stiffness, often accompanied by general prostration and extreme loss of weight. Except for the scleroderma, the symptoms simulated severe generalized arthritis. The differential diagnosis was often difficult, but usually was evident when hardening of the skin was noted and appreciated.

Of the 28 cases in which symptoms of arthritis were present, the original symptoms were in the hands in 12. In many of these the pain in the joints later became more general. In 7 cases there was involvement of all extremities in the beginning. In 3 cases, the condition began in other joints. In 6 cases, there was generalized pain and stiffness in the joints, loss of weight and systemic symptoms. Because of the outstanding arthritic symptoms, roentgenograms of the hands were taken in 16 cases of scleroderma and sclerodactylia. In 6 of these, the roentgenographic evidence was negative. In 4 cases, there was marked periarticular arthritis. In 1 case it was slight. In 2 cases there were destructive changes of the bones of the hands. In 3 cases, there was loss of the distal phalanges of ten, three, and two fingers, respectively; this condition is not infrequent in the late phases in the cases in which the disease is extensive.

In 4 of the cases of the generalized type, the onset of the disease was first noted by the thickening of the skin of the upper part of the trunk and the face, unaccompanied by constitutional symptoms. In 1 of these cases, of the edematous type, edema of the eyelids and face was the first symptom noted.

The occurrence of vasomotor phenomena in the extremities was the next most common initial symptom. This occurred in 16 of the 48 patients with generalized scleroderma (33 per cent). The hands were always involved and in a great many cases the feet were also involved. The severity of the symptoms was exceedingly variable. In the milder cases, only moderate cyanosis was present on exposure to cold. In the more severe cases, there was evidence of all the typical symptoms of Raynaud's disease: the white, blue and red stage and the accompanying pain. In the severe cases, of which there were 3, there was spontaneous gangrene with loss of the distal phalanges following this syndrome. Trophic ulcers of the extremities, especially of the fingers, were fairly common in this group, more so than in the group in which the onset was characterized by arthritic symptoms. Cases of this type of scleroderma with sclerodactylia were not included unless there was scleroderma elsewhere. The associated scleroderma was most commonly found in the thorax and in the face, which was without wrinkles, masklike and stiff.

SCLERODACTYLIA. Brown and O'Leary[8] studied the capillaries of the nailfold in 5 cases of scleroderma with sclerodactylia (Fig. 4). They compared these capillaries with the capillaries in true Raynaud's syndrome with secondary changes in the skin. The most common and almost characteristic change in these cases of sclerodactylia was the presence of giant feathery capillary loops with only a uniform flow of blood. There was little response or change in the flow when the extremity was exposed to cold or friction. Gitlow and Steiner[14] found similar giant capillaries in a case of sclerodactylia which they studied carefully. Brown[7] described the appearance of the capillaries in Raynaud's disease, and called attention to the fact that the morphologic changes in the capillaries are slight but the disturbances in the flow of blood and the response to changes in temperature are more marked. In contrast, the capillaries of the nailfold, in the cases of generalized scleroderma without sclerodactylia, appeared normal.

Sclerodactylia was noted in all except 5 cases of generalized scleroderma. In other words, generalized scleroderma is almost always accompanied (89 per cent) by sclerodactylia. These observations compare favorably with those in the 68 cases of generalized scleroderma reviewed from the literature by Robinson. He found involvement of the fingers in 60 of the 68 cases; in 35 cases the disease appeared first in the hands or fingers.

Sclerodactylia may be said to be of three types: (1) True scleroderma of the fingers with mild vascular changes; (2) the vascular type in which sclerosis of the skin develops after the symptoms of disease of the bloodvessels are noted; (3) a mixed type in which it is impossible to determine whether the dermal or the vascular changes took place first. Moderate experience with scleroderma will permit of the clinical impression as to whether the vascular or the sclerodermic process predominates. A study of the capillaries of the nailfold as a rule substantiates this conception.

Systemic symptoms of a general nature, as has been mentioned, are often outstanding. Evidence of the severity of generalized scleroderma is well shown by the loss of weight, which is often extreme. One patient in this series lost 76 pounds (34.5 kg.). The loss of weight is as a rule closely paralleled by the degree of asthenia, the extent of the disease, the extent of scleroderma, and the constitutional symptoms. Clinical facts of general application were not brought out by the general examinations of these patients. Special studies of the basal metabolic rate and of intoxication by arsenic were made in many cases; the results will be reviewed presently.

CALCIFICATION OF THE SKIN. Calcification of the skin may also be found in extensive cases of generalized scleroderma. Osler and McCrae[29] called attention to it, emphasizing that deposits of cal-

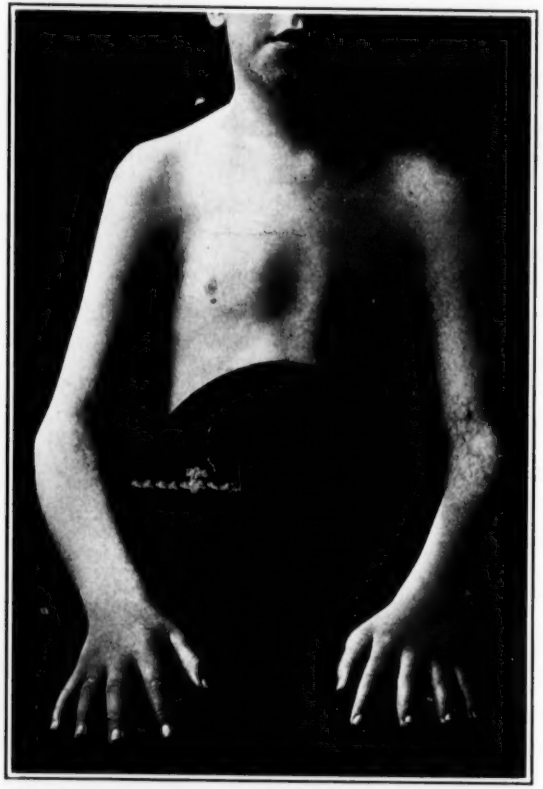

FIG. 1.—Generalized scleroderma.

FIG. 2.—Morphea.

FIG. 3.—Linear scleroderma; developed following a blow to shoulder.

FIG. 4.—Sclerodactylia, showing ulceration of finger tips and changes in the nails.

cium occur usually on the fingers and simulate the tophi of uric acid which occur in gout. Thibierge and Weissenbach presented[28] a case of generalized scleroderma with deposits of calcium. They reviewed adequately 8 other cases reported by various authors, and emphasized that the diagnosis can only be made certain in one of two ways: the demonstration by the roentgenogram of the presence of calcium salts in the nodules, or the ulceration of calcareous nodules and the extrusion of chalky material which may be recognized by chemical examination. In our series, 2 cases of generalized scleroderma with localized calcification were observed. One case was proved by chemical analysis of the extruded chalky material to contain calcium phosphate and calcium carbonate. Biopsy in the second case did not reveal calcium salts which ordinarily may be found deep in the derma, but chalklike material was later discharged from the wound.

Calcification of the skin has often been noted in association with other types of dermatosis. Weidman and Schaffer reported a case in which there were deposits of calcium in almost all elements of the skin, including the cells of the epidermis, arteries, nerves, sweat ducts and sweat glands.

A patient who had all the clinical symptoms of extensive, severe generalized scleroderma was seen at The Mayo Clinic in 1921. The roentgenogram revealed extensive diffuse calcification of the subcutaneous connective tissues, most marked in the extremities. At postmortem examination the presence of extensive generalized inflammatory and sclerotic changes in the muscles as well as in the skin with deposits of calcium phosphate and calcium carbonate, changed the diagnosis to myositis ossificans.

Circumscribed Scleroderma. Circumscribed scleroderma (Fig. 2), also called morphea, on the contrary, is not accompanied by general symptoms or vasomotor phenomena. Usually there are no associated subjective symptoms, and unless the plaques are numerous or their situation is the cause of disfigurement, the lesions go undiagnosed. Scleroderma in bands (Fig. 3), a form of circumscribed scleroderma, if extensive may cause deformity and some atrophy of one or more extremities. A history of trauma frequently precedes the onset of this form of the disease. Ormsby said: "Patches of morphea commonly begin as red or violaceous areas, fingernail to palm size or larger, and increase in size rapidly or slowly. In a variable period of time the center of each patch becomes whitish or yellowish while the peripheral portions of the plaque are purple or violaceous." In 55 cases of circumscribed scleroderma reviewed in this study there was morphea in 38, morphea guttata in 3, and scleroderma in bands in 14. In more than half of the cases the condition began as a single, whitish-pink or scarlike spot; rarely there were several spots. In a few cases the onset was ushered in with localized thickening of

the skin and in 3 cases, with multiple small white spots. Residual brownish pigmentation and the atrophic center of the patch was the rule in these cases.

Osborne, in 1922, reported from The Mayo Clinic 3 cases of morphea associated with facial hemiatrophy. Since then we have observed 3 other cases of morphea and facial hemiatrophy in one of which there was atrophy of the entire right side of the body. The frequent association of morphea and hemiatrophy would tend to corroborate the conception that injury to the nerve from trauma or other causes was a factor in the production of the entity. Hutchinson believed facial hemiatrophy to be a manifestation or residuum of facial morphea. Gans also classified facial hemiatrophy as a manifestation of scleroderma.

Pathology. A study of the histopathology of scleroderma has thrown little light on the cause of the disease. The histopathologic changes, however, indicate that the process is the result of a systemic disease rather than a localized disorder of the skin. The picture is accordingly a secondary manifestation of this disease. The variety of changes of the skin seen in the various types of scleroderma suggests that different noxæ are instrumental in the production of the histopathologic changes. Gans stated that there are three stages in the development of the process: (1) The erythematous or edematous; (2) the indurated; (3) the atrophic. In the indurated stage the most significant changes are noted. In a well-developed case of the diffuse form of the disease Kyrle noted the outstanding changes to be the proliferation of the connective tissue and degenerative changes in the form of homogeneous masses or of individual bundles becoming homogenized. The elastic fibers are not destroyed but may show rarefaction and splintering, and are found between the swollen bundles of collagen. Kyrle stated the belief that the chief pathologic process occurs in the collagen in the nature of colloidal chemical changes.

The histopathologic features of morphea or localized scleroderma are somewhat different from those of generalized scleroderma. The lilac-colored ring noted in morphea is due to the engorgement of the veins of the papillary layer with deposits of pigment about the veins as the result of the stasis. The process extends to and involves the subcutaneous tissue, and the cellular infiltrate is diffuse rather than perivascular. In our study of the cases of both the generalized and localized forms of the disease, the part played by the bloodvessels in the production of the disease seemed an important one. Early in the process many of the bloodvessels are dilated and surrounded with fixed connective-tissue cells, lymphocytes, and a few plasma cells. The intima of the bloodvessels proliferates, becomes swollen, and may almost obliterate the lumen, although the media remains unchanged. The changes in the connective tissue follow as a result of the cellular infiltrate. Later on, it is noted that the bloodvessels

are narrowed and atrophied, and, as the process extends, all of the adnexa of the skin likewise become atrophied.

The pigmentation in the generalized form of the disease is seen at the borders of the sclerodermatous areas and is due to the deposits of melanin in the basal-cell layer of the epidermis and occasionally in the chromatophores of the cutis.

Diagnosis. An established case of generalized scleroderma may be readily diagnosed by one who has had little experience with the disease; however, the recognition of the disease during its early manifestations often presents a difficult diagnostic problem. The onset with symptoms of arthritis or with vasomotor disturbances in the extremities must be borne in mind. In an early case, the patient often complains of stiffness of the skin before the sclerosing process is visible or palpable. At this time the limitation of motion, the decrease in the normal wrinkles of the skin, a sheen of a slightly waxy hue and the loss of expression, if the face is involved, are among the early manifestations. It is also at this time that the sclerodactylia may become manifest although it may require observation for several months before a definite diagnosis is possible. In the advanced case with sclerodactylia the hands are stiff and cold. The skin of the hands is hard, suggesting the wax hand of a moulage, ivory-yellow and unwrinkled. On palpation and pinching, the fixedness suggests the skin of a pig. If the face is involved it presents a stiff masklike appearance, as in Parkinson's disease. The normal furrows in the skin are ironed out and the patient often cannot wrinkle the forehead. Expressions of emotion are absent, the opening of the mouth is limited, due to sclerosis of the skin of the cheeks, and the speech may be indistinct. The skin of the torso and legs presents varying degrees of induration and sheen, depending on the extent of involvement.

The early manifestations of generalized scleroderma are often erroneously diagnosed chronic arthritis, not only because of the pain and stiffness of the joints, but because roentgenologic changes suggestive of those in chronic arthritis are often found in the hands of patients who have sclerodactylia. Therefore, mild roentgenographic changes must be disregarded in the diagnosis. In the cases in which vasomotor disturbances are prominent, the distinction from Raynaud's disease is often difficult, and unless the masklike facies or other evidence of scleroderma elsewhere is present, the diagnosis cannot be made without subsequent observation. For the present, patients who present outstanding vasomotor phenomena of the hands with slight induration in the skin of the hands and no evidence of scleroderma elsewhere, must be considered as having Raynaud's disease. It is in this group that studies of the capillaries of the nailfold will often permit of a differential diagnosis early in the course of the disease.

The edematous variety of generalized scleroderma, which is

uncommon, may be confused with other conditions causing edema of the face. The brawniness of the edema and the presence of scleroderma and atrophic changes in the skin elsewhere on the body will ordinarily make the diagnosis clear. In the few cases in which the fingers are not involved in diffuse scleroderma, the diagnosis is made on the physical changes in the skin, particularly of the face and the upper part of the thorax and neck.

In the cases of generalized scleroderma which have produced atrophy of the skin, distinction must be made from acrodermatitis chronic atrophicans and other forms of idiopathic cutaneous atrophy. The tight "straffe" atrophy of scleroderma is readily distinguished from the loose, tissue-paperlike atrophy of idiopathic atrophy. Wise considered the relationship of the two diseases and expressed a conception with which we are in accord.

As has been mentioned in commenting on calcification of the skin in scleroderma, generalized dermatomyositis may resemble generalized scleroderma closely. Deep biopsy will show the inflammatory and sclerotic changes in the muscles.

Extensive pigmentation of the skin which often accompanies scleroderma may suggest the Addisonian syndrome. The absence of the features of Addison's disease, namely, marked asthenia, low blood pressure, and pigmentation of the mucous membranes, and the lack of scleroderma will distinguish Addison's disease from scleroderma.

Scleroderma in infants is rare. Lieberthal has pointed out the relative benignity of scleroderma in infants compared to sclerema neonatorum. In this disease the irregularly distributed, well-defined plaques of induration which occasionally have cystlike centers, besides diarrhea, dehydration, and constitutional symptoms often lead to death in a few weeks. Infants with scleroderma, however, usually recover without sequelæ.

The diagnosis of the circumscribed varieties of scleroderma offers fewer difficulties. Morphea usually presents the typical, atrophic ivory or silvery, often pigmented patch with a violaceous halo. It may be quite extensive, involving much of the torso. It is usually confused with still rarer dermatosis, especially with the group of idiopathic types of atrophy, and with atrophic lichen planus. Scleroderma in bands is similar to morphea. It often causes deformities and marked atrophy of the extremity involved, and therefore comes to the attention of the orthopedic surgeon. The guttate type of circumscribed scleroderma is rare and is to be distinguished from other benign types of atrophic dermatosis.

Sex Incidence. A preponderance of females was noted in most of the reports in the literature. Most writers group generalized and circumscribed scleroderma together, which may account for some of the disparity in the series reported. The incidence varies greatly. Thus, Castle reported cases of 11 females and 1 male,

Sequeira reported cases of 18 females and 4 males, Cockayne reported from the literature 104 cases in females and 28 in males, Hutchinson noted 16 females and 11 males in his series, and in Osler's[28] 8 cases of generalized scleroderma, 3 were females and 5 were males.

Fig. 5 shows the sex distribution of generalized and circumscribed scleroderma in our group. In both varieties females predominate; 58 per cent of the cases of generalized scleroderma were in females, and 72 per cent of the cases of circumscribed scleroderma were in females. No explanation of this fact has been made, but the great disparity in sex incidence can scarcely be ascribed to coincidence. Circumscribed scleroderma, particularly, has a predilection for the female.

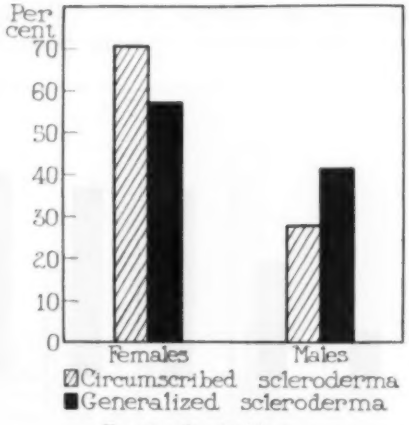

FIG. 5.—Sex incidence.

Age Incidence. Apparently no age is exempt, but adults are more often affected. Lieberthal reported a case of scleroderma in an infant, aged nine days. Goodman reported a case of generalized scleroderma in a girl, aged nine years. He reviewed 16 cases from the literature taken mostly from Levin and Heller's monograph on scleroderma. Cockayne noted the report of 102 cases of scleroderma in children aged less than fourteen years. In Osler's[28] cases of generalized scleroderma, the ages ranged from twenty-one to forty years, and in Hutchinson's cases, which were mostly of circumscribed scleroderma, the ages ranged from ten to seventy-five years.

In our series, the ages ranged from eighteen to sixty-six years in generalized scleroderma and from three and a half to sixty-seven in circumscribed scleroderma. Fig. 6 shows clearly the relative and absolute preponderance of circumscribed scleroderma in the first three decades, and the reverse holds true for the fourth, fifth and sixth decades. Both, however, have their maximal incidence in

adult life. A peculiar observation was the great number of cases of scleroderma in bands occurring in the early decades of life. Thirteen of 14 cases occurred in the first three decades.

Etiology. The cause of generalized scleroderma is unknown and no notable advance has been made since the time of Hutchinson, in spite of much study and investigative work, as evidenced by the voluminous literature on the subject. Boardman recently reported a comprehensive review of the literature on the etiology of the disease from which conclusive deductions are not possible. Dysfunction of the thyroid gland has received most attention, but none of the endocrine glands has been slighted. Nervous shock, exposure, infections, syphilis, and pregnancy have likewise been thought to have a causative relation. Chronic intoxication by arsenic has also been proposed as an etiologic factor. Because of the vasomotor symptoms in the extremities in many cases, with the simula-

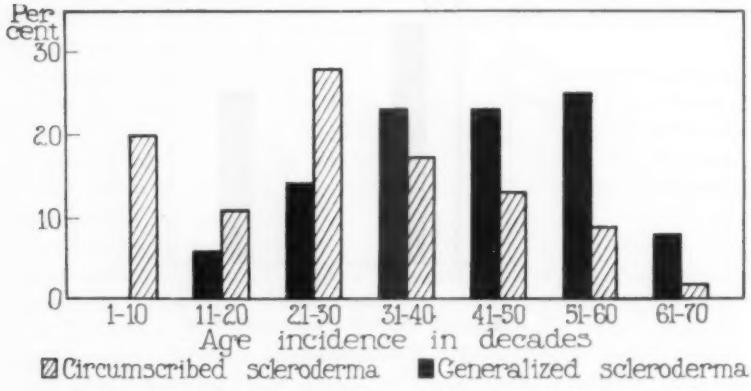

FIG. 6.—Age incidence in decades.

tion of Raynaud's disease, vascular neurosis has entered into the consideration. The hypothesis that it is a disease of unknown varied etiology in which noxæ affect chiefly the bloodvessels and collagen of the connective tissue of the dermis, has been proposed by many authors. This hypothesis is based almost entirely on the histopathologic changes in the disease, and is therefore tenable and, to say the least, incapable of disproof at the present time. In a search for possible etiologic factors, special laboratory studies were undertaken to determine the part played by the thyroid gland, changes in blood sugar, the pituitary gland, and arsenic in the urine, in the production of the disease. Likewise particular effort was directed toward the eliciting of a history, either recent or remote, of one of the infectious diseases. The accumulated data are presented in detail.

Castle recently reviewed the literature on the endocrine causation of scleroderma, laying special emphasis on dysfunction of the

thyroid gland. He concluded that the cause is unknown, but that the endocrine glands and the nervous system are etiologic factors. Osler[28] was unfavorably impressed with the results of treatment with thyroid extract. Roques, on clinical examination of 31 cases of generalized scleroderma, found that the thyroid gland was small or imperceptible in 14 cases, hypertrophied in 8, and normal in 9. In his review of 67 cases, including his own, he found that 63 per cent of the patients were benefited by treatment with thyroid extracts. Hyde and McEwen and Foerster also commented on the relationship of scleroderma and dysfunction of the thyroid gland. Alquier and Touchard found perivascular sclerosis in the thyroid gland as well as in most other tissues in 1 of 2 cases of generalized scleroderma which came to necropsy. Hektoen and Wells found

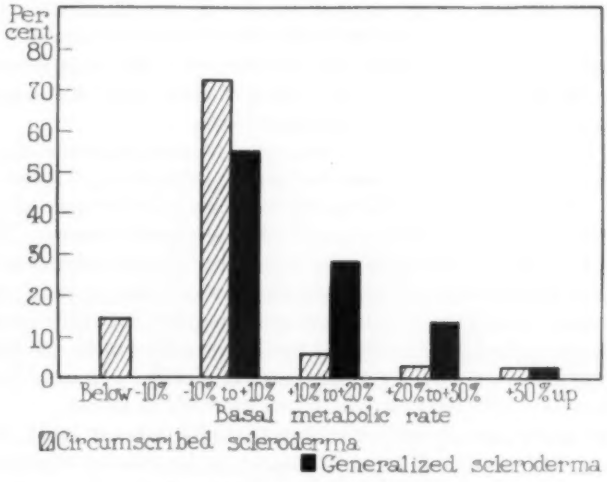

FIG. 7.—Basal metabolic rate.

marked deficiency in the amount of iodin in the thyroid gland at necropsy in a case of generalized scleroderma. Sequeira observed the development of scleroderma in a case of myxedema in which the latter condition was controlled by treatment of the thyroid gland. In Longcope's recent series of 7 cases, the basal metabolic rate was below normal in 3; the lowest rate was −23 per cent.

In our series of cases of generalized scleroderma, dysfunction of the thyroid gland was especially searched for. Determinations of the basal metabolic rate were made in 38 cases of generalized scleroderma. All of these determinations were rechecked to avoid error. In many cases repeated checks were made to determine the effect of administration of thyroxine and dried thyroid gland on the metabolic rate. For purposes of tabulation, the lowest determination of the basal rate was taken (Fig. 7).

In none of the cases of generalized scleroderma was the basal rate below normal. Neither were there any cases in which there was clinical evidence of hypothyroidism. In 17 cases (45 per cent), the basal rate was more than +10 per cent. In 7 of these cases (18.4 per cent of the total) there was evidence of hyperthyroidism, in 2 of which adenomatous goiter with hyperthyroidism was present, and in 1 case, typical severe exophthalmic goiter. In 3 cases the diagnosis of exophthalmic goiter was suggestive but not conclusive. In the seventh case adenomatous goiter with elevation of the basal metabolic rate and suggestive clinical signs of hyperthyroidism were present.

Similar but less extensive studies of the basal metabolic rate were made in 33 of the 55 cases of circumscribed scleroderma (Fig. 7). It will be seen that rates slightly below normal were present in 5 cases (15 per cent of the total) of circumscribed scleroderma. In 4 cases (12 per cent) the rate was above normal. In 2 of these cases hyperthyroidism was present, in 1 case in a severe form with a basal metabolic rate of +64 per cent, and in the other an adenomatous goiter with hyperthyroidism.

Fig. 7 shows that in most of the cases of generalized and circumscribed scleroderma the basal metabolic rates were within normal limits. The few cases in which the rates were below normal approximate the average incidence in a similar unselected group. There is, however, a higher incidence than normal of dysfunction, in that in 7 cases of generalized scleroderma there was either hyperthyroidism or adenomatous goiter with hyperthyroidism besides the scleroderma. A cause and effect relation could not be brought out in the taking of the history, or in the study of the cases clinically. In only 2 cases of circumscribed scleroderma was hyperthyroidism noted.

Other endocrine glands have been thought to be at fault. Castle, in his review, reported a case thought to be due to suprarenal insufficiency in which a graft of the suprarenal gland was attempted without success. Longcope reported a case in great detail in which there was bronzing, asthenia, low blood pressure and low blood sugar. He remarked on the similarity to Addison's disease. In our series, definite or presumptive evidence of Addison's disease could not be elicited. Pigmentation was frequently extreme and asthenia and loss of weight were marked in some cases, but never enough so that a diagnosis of insufficiency of the suprarenal gland could be considered seriously. The blood pressure was almost always normal; in a very few cases it fell as low as 105 mm. of mercury. Pigmentation of the mucous membranes was not noted in any instance.

Longcope also reported the presence of marked hypoglycemia with attacks simulating those following overdosage of insulin in one of his cases. The blood sugar in the others he reported was near the lower limits of normal. In a case reported by Gitlow and Steiner, the blood-sugar curve was normal. Knowles and Ludy reported a

case of diabetes occurring in a patient with generalized morphea. In their case the condition of the skin improved when the diabetes was controlled. In 2 cases of our series, circumscribed scleroderma was associated with mild diabetes and fasting blood sugar of 513 and 221 mg. for each 100 cc., respectively. Studies of the blood sugar were made in 2 cases of generalized scleroderma. The amounts of glucose found were 110 and 98 mg. for each 100 cc., respectively, which is well within normal limits. These data are of course fragmentary, but hyperglycemia with mild diabetes was found in 2 cases, whereas hypoglycemia was not found in the 2 other cases studied.

Disease of the pituitary gland has been suggested by some writers as a possible cause of scleroderma, but the evidence presented is purely hypothetical. In our series, there was no clinical evidence of pituitary changes in any of the cases. Roentgenograms of the pituitary fossa were made in 4 cases, and were found to be negative.

Within the last few years, chronic intoxication by arsenic has also been suggested as a cause of scleroderma. Ayres found arsenic in the urine of 3 patients with generalized scleroderma. Myers and his coworkers emphasized the frequency of arsenic in the urine in scleroderma, but they also found arsenic in many other cases of dermatosis and thus seriously weakened the argument that it was a causative agent. Brooke and Roberts reported on arsenical eruptions seen in Manchester, England, caused by arsenic in cheap beer; they did not observe cases of scleroderma. They saw almost every variety of skin eruption caused by arsenic. In our series, the possibility of intoxication by arsenic was investigated in 23 cases. The tests were usually done on the twenty-four-hour specimen of urine.

The finding of arsenic in the urine of patients with generalized scleroderma was exceptionally difficult to evaluate because medication with arsenic is so frequently given for this disease and also because arsenic was not uncommonly found in the control case. This fact was best brought out by the cases in which large amounts of arsenic were found, and in which arsenic had been given almost uniformly. There were 2 of the 48 cases of generalized scleroderma in which it seemed that chronic poisoning by arsenic was a precipitating or a possibly causative agent of the disease. In the first case, that of a woman in charge of a paint and wallpaper store, there was simultaneous onset of sclerodactylia with scleroderma and arsenical peripheral neuritis. The peripheral neuritis disappeared eventually, but the scleroderma remained. In the second case, that of a worker in a paint factory, scleroderma, mild exophthalmic goiter and symptoms of heavy metal poisoning developed simultaneously. The man was not anemic and lead was not present in the urine. However, arsenic in pathologic amounts was found in the urine. The basal metabolic rate was, moreover, +20 per cent. Osterberg

expressed the belief that traces up to 2 mg. of arsenic in a twenty-four-hour specimen of urine are frequently found in normal persons. This is especially true of heavy smokers. More than 3 mg. of arsenic indicates ingestion, the source of which may not be determined although it is usually found to be due to medication, ingestion of food, cheap chocolate in particular, or occupational exposure to arsenic.

As a control series, determinations of arsenic were made in 19 cases of various other cases of dermatosis. In all of these, less than 3 mg. of arsenic was found in the twenty-four-hour output of urine except in 1 case, in which there was a definite history of the ingestion of arsenic.

Determinations of arsenic were made on the urine in 6 cases of circumscribed scleroderma, in 4 of which arsenic was present in appreciable amounts, from 2.8 to 8.4 mg. in each twenty-four-hour specimen, while in 2 cases the urine was negative for arsenic. An etiologic relationship between generalized or circumscribed scleroderma and chronic poisoning by arsenic could not be established in this study.

Certain authors ascribe systemic infections as the causative factor, either as acute infection simultaneous with or just preceding the onset, or chronic infection such as syphilis.

In our series, acute general infections immediately preceded or occurred with the onset in 6 (12.5 per cent) of the cases of generalized scleroderma. It has been suggested that the dermal symptoms in generalized scleroderma are an expression of a severe, general systemic disease. The preceding infection in these 6 cases was diagnosed influenza three times, tonsillitis twice and erysipelas once. In circumscribed scleroderma general infection occurred only in 2 cases, which were diagnosed poliomyelitis and scarlet fever, respectively.

Of the chronic infections, syphilis, probably because of its ubiquity, has been stressed as a causative factor. Murray-Will, and Audry and Chatellier have emphasized the significance of syphilis as a cause of generalized scleroderma. In our series, clinical investigation for syphilis was carried out, and Wassermann tests were done on 82 of the patients with generalized or circumscribed scleroderma. Two patients with generalized scleroderma had syphilis, and 2 patients with circumscribed scleroderma also had syphilis. An etiologic relationship could not be elicited, and the therapeutic test for syphilis did not offer relief for the scleroderma. The incidence of syphilis in cases of scleroderma is about the same as the general incidence of syphilis in other diseases.

A history of trauma was obtained in 11 of the 14 cases of scleroderma in bands. The most frequently observed site for this form of the disease is the upper extremity, with the history of an injury or blow to the corresponding shoulder or side of the neck. Other

instances of injury to the forearm, leg, or side of the head have been followed by the linear type of scleroderma. Trauma of practically all types has been suggested as etiologic factors in the disease.

Prognosis. The prognosis, as to cure, in cases of generalized scleroderma is poor. The protracted course of the disease is illustrated in our series by the fact that 26 patients (54 per cent) with generalized scleroderma had had the disease more than two years before they were seen at The Mayo Clinic. Of the 8 patients who died, the average duration of the disease was more than four years, with a maximum of twelve years and a minimum of one year.

Of the 48 patients with generalized scleroderma, the condition of 14.5 per cent was slightly improved, of 10.5 per cent decidedly improved, and of 6.3 per cent almost completely cured clinically. An analysis of the cases in which the patients recovered showed that the condition was of the edematous type of generalized scleroderma.

It is to be borne in mind that spontaneous remission is noted occasionally in the generalized forms and frequently in the circumscribed forms of the disease; this is a factor to be considered in the interpretation of the value of all types of treatment.

Acute systemic infections play a prominent part in the death of patients with generalized scleroderma, although cardiorenal insufficiency seemed to play the major part in our series of cases.

The prognosis in circumscribed scleroderma is good. There is nothing to indicate any serious sequelæ or severe constitutional symptoms. The outlook in respect to the changes of the skin, however, is not good; the resulting atrophy is permanent and of cosmetic concern. The progress of the circumscribed form of the disease is more readily controlled but usually it was arrested spontaneously with relatively little involvement of the skin. In young persons scleroderma in bands may cause deformities of one or more extremities which must be treated by orthopedic measures. Circumscribed scleroderma is essentially benign, affects the skin primarily, and is not associated with severe systemic disturbances.

Treatment. As has been indicated in considering the etiology of the disease, extracts of the thyroid gland have long been used in the treatment of scleroderma. In our series, the extracts were given in cases in which the basal metabolic rate was below the average. The preparations used were either thyroxine, 4 to 8 mg., or desiccated thyroid gland, 67 to 125 mg. The dosage of the drug was regulated to keep the basal metabolic rate between 0 and +10 per cent. The results of the use of the various preparations of the thyroid gland do not admit accurate tabulation or analysis because other therapeutic measures were undertaken simultaneously. The results of treatment with the preparations of the thyroid gland were disappointing in the group as a whole. In cases of hyperthyroidism, thyroidectomy was done without apparent change in the scleroderma and, likewise, the use of compound solution of iodin in the cases of

exophthalmic goiter resulted in improvement in the general symptoms but without effect on the scleroderma.

It is our belief that the value of extracts of the thyroid gland in the treatment of scleroderma is dependent not on the specific influence of the extract or the fact that the gland is manifesting hypofunction, but on the influence that the extracts exert on increasing the blood supply in the cutaneous vessels.

When arsenic was suspected of being a factor and in many other cases in which appreciable amounts of arsenic were found in the urine, sodium thiosulphate was given intravenously in repeated courses of 6 to 20 injections, but without noticeable improvement of the scleroderma.

Physiotherapeutic measures seemed to offer the outstanding symptomatic relief in this series. The treatment was of the simplest type consisting of ordinary baking followed by massage and active and passive exercise. Treatment by ultraviolet light seemed to be an adjuvant. The removal of unquestionable foci of infection was advised on general grounds.

When possible the patient was advised to move to a warm, sunny, dry, equable climate such as that of Arizona, New Mexico, Florida or southern California. A study of the returns from the follow-up letters would indicate that this was a major factor in the improvement of a large proportion of those who reported amelioration of symptoms. The patients in this series who showed the greatest improvement were those who moved to the warmer climate, who persisted faithfully in the use of dry heat locally, followed by massage and passive exercises, and who continued to take extract of the thyroid gland purely on empiric grounds.

Recently Adson and Brown made a preliminary report of the value of thoracic sympathetic ganglionectomy as a method of treatment for sclerodactylia. Observation and further experience with this method of treatment are necessary, although at this time it seems that the vascular type of sclerodactylia, the type in which the Raynaud syndrome predominates in the development of the scleroderma of the fingers, will show the most improvement following this operation.

Summary. A series of 48 cases of generalized scleroderma and 55 cases of circumscribed scleroderma was studied. In more than half of the cases of the generalized type, arthritis preceded or occurred simultaneously with the development of the scleroderma. In 33 per cent, the onset was preceded by varying degrees of vasomotor disease in the extremities. In addition, in the study of etiology, general infectious disease, such as influenza, or dysfunction of the glands of internal secretion, particularly of the thyroid gland, or arsenism, were observed. Sclerodactylia was observed in 89 per cent of these cases. The expectancy of life is difficult to determine, although seven years was the average length of life in this group, and symptomatic cure was obtained in 6 per cent only.

Morphea, or localized scleroderma, is a benign disease, whereas generalized scleroderma is a disabling and usually a fatal one. There is practically no parallelism between the two diseases in onset, course, clinical appearance, and prognosis, although the dermal changes are similar. Occasionally both diseases are present in the same patient.

Although the accumulated evidence does not contribute any established facts as to etiology, it warrants the belief that generalized scleroderma is the cutaneous manifestation of systemic disease in which changes in the vascular system play a leading part. The group in which the onset of the scleroderma seems definitely related to acute systemic infectious disease is offered symptomatic relief by medical and surgical treatment.

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REVIEWS.

IMMUNITY IN INFECTIOUS DISEASES. By PROF. A. BESREDKA. Pp. 364. Baltimore: The Williams & Wilkins Company, 1930.

IN this treatise, the author reviews various theories of immunity and attempts to clear up a number of misconceptions concerning the relations between virus and organism which are still circulating alongside facts solidly established. He points out that these relations vary not only with the nature of the germs, but very often with that of the cells which they invade. Recent acquisitions to the subject of immunity are presented in the form of "studies" which are more or less independent of one another but nevertheless form an integral whole and add greatly to our general knowledge of the subject of immunity.

The book comprises fifteen chapters, dealing with problems which include investigations concerning the bactericidal power of the leukocytes, bacterial hemolysins, microbal endotoxins, vaccination by various methods and the function of the skin in infection and immunity. In addition to reviewing the older theories of immunity, the author adds much to our knowledge of the subject with his theories and experimental evidence indicating that in the majority of affections, the cause of immunity seems to be more clearly bound up with the presence of antivirus in the region of receptive cells than that of antibodies in the blood. To quote the author: "Antivirus therapy—preventive or curative—founded upon the principle of local immunization without antibodies, has its position marked out in a number of morbid processes, which elude the action of serotherapy or of vaccine-therapy as they are practised today."

W. K.

LES SYNDROMES DOULOUREUX DE LA RÉGION ÉPIGASTRIQUE. Vols. I and II. By RENÉ A. GUTTMANN. Pp. 1140; 542 illustrations. Paris: Gaston Doin & Cie, 1930. Price, 200 francs.

THESE paper-bound volumes represent a critical study of the causes of pain in the epigastrium, made by an internist attached to Professor Gosset's Clinic. As Professor Gosset points out in his preface, the author has been able to make extensive clinical and radiologic studies and then to follow the patients to the operating

table where the exact pathology was exposed. The first chapter describes a definite method for the clinical study of epigastric pain in order to make it useful in leading to a diagnosis.

Various disease entities (ulcer, tumor, gall bladder disease, and so forth) producing pain in the epigastrium are then described separately and completely. No attempt is made to describe the etiology but the clinical signs and symptoms are given in considerable detail. Radiologic findings are well outlined and illustrated with very fine reproductions of typical films. Cases are briefly reported illustrating the text. The latter part of each section is devoted to a description of the treatment of the disease under consideration. The author gives first the treatment he usually employs and then a fairly complete résumé of the therapeutic measures described in the literature, the therapeutic point of view naturally differing in many respects from that of American authors. For example, in the treatment of cholelithiasis is given a list of the various springs and the pathologic conditions which may be benefited, such as, "Gall stones with relatively recent hepatic colic: Vitelle. Stones without recent hepatic colic: Vichy. Stones in obese patients: Brides-les-Bains, and so forth."

On the whole the work should prove most valuable to those interested in gastroenterology, the chapters on ulcer syndromes and the syndrome of the gall bladder standing out as especially well written. L. F.

PROCEDURE IN EXAMINATION OF THE LUNGS. By ARTHUR F. KRAETZER, M.D. 125 pages; 15 illustrations. New York: Oxford University Press, 1930. Price, $2.00.

THOSE who teach physical examination of the chest will welcome Dr. Kraetzer's book as the opening gun on Fort Sumter. To students and physicians it will be a Baedeker in a too often undiscovered country. The plan of the book is to present the method of approach to pulmonary diagnosis, showing how to elicit physical signs and when elicited how their true meaning should be induced. Beginning with a chapter on the "Actual Sounds," one is conducted through the hills and valleys of inspection, palpation and auscultation until the promised land of clear interpretation is reached. The chapter on "Diminished Breath Sounds" is the high point of the book. The desire of the author to eliminate Graeco-Latin terms from our chest parlance is excellent though not carried to its logical conclusion, and when he speaks of "the relative bronchiality of the apices," the Reviewer admits a complete bewilderment. Nevertheless, this is a book which will ease the path of student and teacher equally. C.-F. L.

THE SCIENCE OF NUTRITION SIMPLIFIED. By D. D. ROSENWARNE, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 314; 7 illustrations. St. Louis: C. V. Mosby Company. Price, $3.50.

AFTER a brief discussion of the underlying principles of chemistry and physiology, the author presents clearly and simply the needs of the body for the various classes of food materials. The importance of eating a diet composed of a large number of foods is fully explained. There are, however, some statements the accuracy of which could be questioned. At the end of the book is inserted a table of food values.

The presentation of any scientific subject in a manner to be understandable by individuals untrained in science is always a difficult problem, and it is questionable if the author has entirely succeeded in this case. Nevertheless, anyone unfamiliar with the subject of nutrition could obtain many new ideas and facts by a study of this book. J. J.

CLINICAL OBSTETRICS. By PAUL T. HARPER, PH.B., M.D., SC.D., F.A.C.S. Pp. 629; 84 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $8.00.

THIS book describes the normal mechanism of labor and its conduct, with a discussion on obstetric analgesia, and then proceeds to a detailed presentation of the prominent abnormalities of pregnancy, labor and the puerperium, with a dissertation on the operative procedures that may be necessary for the various abnormalities mentioned. It is not a book for the undergraduate student: it presupposes a broad knowledge of the basic principles of obstetrics, and is unusually well suited to the needs of the general practitioner who is actively engaged in obstetrics, giving him a well-balanced description of the problems he may meet, an analysis of them, and a clear and concise method of attack. The personal element in such a manner of preparing a book of this nature may cause those whose lines of procedure are already well defined to probably object to the author's recommendations, but they are safe, sane and concisely expressed, and a comparison of methods hurts no one. Particularly was the Reviewer impressed with the presentation of the normal mechanism of labor, the discussion of the relative merits of version and high forceps in occiput posterior presentations, his sane attitude toward routine versions and his treatment of breech presentations, and the effort to show that toxemias of pregnancy need a rational therapy for the individual case and not a blind standardized set of orders. The illustrations are mostly line drawings but the correlation with the text is excellent. The book is highly recommended.

P. W.

HEMORRHOIDS, THE INJECTION TREATMENT AND PRURITUS ANI. By LAWRENCE GOLDBACHER, M.D. Pp. 205; 31 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $3.50.

THE author advocates the treatment of internal hemorrhoids by the injection of 8 to 10 cc. of 5 per cent phenol in cottonseed oil. For thrombosed or external hemorrhoids surgery is indicated. No recurrences have been observed and there have been no ill effects from the injections. A special slotted anoscope has been devised to facilitate the technique. The method is painless and hospitalization of the patient is unnecessary. However, experience is essential to secure uniformly good results. A small series of cases of intractable pruritus ani have also been treated by injection. The results have been gratifying to the author.

The contents of this book might readily be condensed into one or two papers of average length by the omission of much repetition, needless summaries of short chapters and a series of unilluminating case reports. This verbosity, however, is the main fault. It is a clearly written, practical manual on a method of treatment which appears to have produced excellent results in the hands of an enthusiastic adherent. E. E.

DISEASES TRANSMITTED FROM ANIMALS TO MAN. By THOMAS G. HULL, M.D. Pp. 350; 29 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, $5.50.

THE preface states that "Diseases which may be transmitted from animals to man immediately concern—the veterinarian, the physician, the laboratorian and the health official—each—engaged with a different phase of the problem—and viewing it from a different angle." "The present volume was written with each of them in mind, to afford a common meeting ground where each might understand the problem of the other, and thus, through concerted effort reduce the number of infections which man contracts from animals."

The work is divided into five sections: I. Diseases of Domestic Animals and Birds—Tuberculosis, Anthrax, Foot and Mouth Disease, Malta Fever and Contagious Abortion, Milk-sickness, Actinomycosis, Smallpox and Cowpox, Glanders, Rabies, Psittacosis, Food Poisoning, Swine Erysipelas and Affections Caused by Animal Parasites. II. Rodent Affections—Plague, Tularemia, Spirochetal Jaundice, Rat-bite Fever, Rocky Mountain Spotted Fever. III. Human Diseases Spread by Animals—The Relations of Human Infections to Animals—Septic Sore Throat, Diphtheria, Scarlet Fever, Other Human Diseases Sometimes Contracted by Animals. IV. Animals as Passive Carriers of Disease Organisms—Botulism, Tetanus, Gas Gangrene. V. A Review of the Rôle

Played by Each Animal in the Spread of Disease—The Rôle of Cattle, Horses, Swine, Sheep, Goats, Dogs, Cats, Rats and Mice, Poultry, Birds and Wild Game. Then lengthy Bibliographical and General Indexes. There are also 29 illustrations, consisting of photographs and maps.

Each of the subjects is excellently and systematically treated, with a degree of conciseness and thoroughness that are rarely met together; the bibliographical references number well over 800, so that though the book is small it is almost encyclopedic in character, and can be most highly recommended. J. McF.

THE MECHANISM OF THE LARYNX. By V. E. NEGUS, M.S. (LOND.), F.R.C.S. (ENG.). Pp. 528; 160 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $13.50.

THIS book is really a noteworthy achievement representing the results of a decade of time-consuming and laborious investigation. The author has assembled thousands of facts, recorded the results of numerous experiments and stated his ideas, many of which are original and unique, in a most logical and convincing manner. Sir Arthur Keith, in his introduction, compares the author's methods to those of Hunter and Darwin. Every laryngologist, no matter how experienced, will have his horizon widened and his interest in the larynx stimulated by this book. The larynx is considered from all possible angles. The facts dealing with its evolution, comparative anatomy, responses to environment, and physiology, are sanely and clearly assembled. From the primitive larynx of Dipnoi the author traces laryngeal development to the highest mammals. The book is well organized and contains at the end of each chapter a conclusion and summary which aids greatly in crystallizing the facts already presented in detail. K. H.

BOOKS RECEIVED.

NEW BOOKS.

The Surgical Clinics of North America, Vol. 10, No. 2 (Chicago Number, April, 1930). Pp. 252; 72 illustrations. Philadelphia: W. B. Saunders Company, 1930.

The International Medical Annual, 1930. By Various Contributors. Edited by CAREY F. COOMBS, M.D., F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 508; 115 illustrations. New York: William Wood & Co., 1930. Price, $6.00.

Preserves its usual high standard of wise selection and practical value.

*Tuberculosis Among Children.** By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P. Pp. 208; 43 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, $3.50.

The Morphine Habit and Its Painless Treatment. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (OXON.). Pp. 94. London: H. K. Lewis & Co., Ltd., 1930. Price, 5/–.

"It is the object of this small volume to suggest that the psychic and somatic rehabilitation of the addict who commonly presents himself for treatment is a simpler and more hopeful task than it is credited to be; and that the avoidance of withdrawal-shock, to use the term in its widest sense, plays a more important part in the ultimate issue than is generally supposed."

*Gynecology for Nurses.** By GEORGE GELLHORN, M.D., F.A.C.S. Pp. 275; 145 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $2.00.

I Fondamenti della Biotipoligia Umana. By MARIO BARBÁRA. Pp. 122; 3 illustrations. Milano: Soc. An. Instituto Editoriale Scientific, 1929.

Transactions of the American Otological Society, Inc., Vol. XIX. Pp. 217; 13 illustrations. New Bedford, Mass.: By the Society, 1929.

Sindrome de Oclusión Coronaria. By ANTONIO BATTRO. Pp. 214; 111 illustrations. Buenos Aires: Libreria "El Ateneo," 1930.

Æsculapius. A One-act Play. By BARBARA RING. Pp. 40. Boston: Walter H. Baker Company, 1930.

An interesting item for Osler's Bibliotheca Literaria.

The Medical Directory of the National Medical Association of China, 1930, Second Biennial Issue. Issued on the Occasion of The Eighth Biennial Conference, February 2 to 8, 1930, Shanghai. Pp. 241.

NEW EDITIONS.

Varicose Veins. By H. O. MCPHEETERS, M.D., F.A.C.S. Pp. 233; 45 illustrations. Second edition. Philadelphia: F. A. Davis Company, 1930. Price, $3.50.

Additions concerning the Trendelenburg and Bernstein tests, also a few modifications of the technique. The work is useful, as was the first edition, to those contemplating injection treatment of varicose veins.

Obstetrics for Nurses. By JOSEPH B. DELEE, A.M., M.D. Pp. 645; 269 illustrations. Ninth edition. Philadelphia: W. B. Saunders Company, 1930. Price, $3.00.

"The type matter has been completely reset and the illustrations with few exceptions were done over" . . . "Emphasis has been placed on the care of confinement at the home of the patient."

Dental Formulary. By HERMAN PRINZ, A.M., D.D.S., M.D., Sc.D., D.M.D. (COLOGNE). Pp. 364. Philadelphia: Lea & Febiger, 1930.

"The complete exhaustion of the third edition of the *Dental Formulary* has necessitated a thorough revision of the entire subject matter. Many important additions have been made which may prove of interest to the dental practitioner and allied readers. Formulas which have lost their merit have been discarded, most of the new material has been added on solicitation of professional friends from all parts of the world."

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Gastric Secretion in Cancer of the Stomach.—POLLAND and BLOOMFIELD (*Bull. Johns Hopkins Hosp.*, 1930, **46**, 307) write that satisfactory studies of the gastric secretions in carcinoma of the stomach have not been attained because of the presence in the hypomotile stomach of the products of stagnation, of blood or pus. The physician is confronted with a mixture of different substances which obscure completely the determination of the character of the gastric juice which the stomach is secreting. Their present study is made on a relatively small series of cases with cancer of the stomach (19 in all) who were observed in the hospital. They obviated the possibility of stagnant gastric contents being present by washing out the stomach for several days before the examination was done. The patient was starved for the preceding eighteen hours. A duodenal tube was introduced into the stomach, and the total secretions were withdrawn continuously over successive ten-minute periods. After two such periods histamin was injected and the gastric contents were gathered for from three to six further ten-minute intervals. The material that was obtained was studied grossly as to its quantity, the presence of acidity (titratability), the pH and ferment content. The authors report on their results somewhat as follows: Only a small amount of gastric secretion was removed. This was grossly abnormal in appearance. The typical material was made up of tenacious mucoid gray or brownish fluid, frankly bloody at times and in two instances foul. When there were normal acid values the juice was in no ways remarkable. The maximum quantity obtained was practically never over 10 cc., usually from 1 to 5 cc. There was usually an absence of titratability using the dimethyl indicator. Only three of the patients had figures approaching anywheres near the normal. In no instances were acid values above normal encountered by these authors in patients with cancer. The pH of the gastric contents tested colorimetrically in some instances showed

that traces of acid were being secreted, although the dimethyl test was negative. Five cases were tested for pepsin. In several instances, despite the fact that there was no free acid, pepsin was still demonstrable. The secretion of mucus was considerably reduced. The authors next considered the question of the cause of changes in the gastric secretion in cancer of the stomach, reviewing the literature to show how these changes have been explained by other observers. In summarizing their article, they lay stress on the deficiency of the gastric juice, as in no instance did they encounter acidity or volume of secretion above the average. They also make the statement that "all evidence points away from the occurrence of cancer in the previously normal stomach, although this may occur in a very small percentage of cases. Cancer appears to arise almost always on the basis of an already existing lesion, usually a chronic gastritis, less frequently a peptic ulcer."

SURGERY

UNDER THE CHARGE OF

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Postoperative Fat Necrosis of the Breast.—KING (*J. Coll. Surg. of Australasia*, 1929, **2**, 233) says that Lee and Adir laid down certain criteria for its clinical diagnosis and its occurrence in an adipose breast, usually in an obese person, a history of trauma, painless and stony hardness of the mass, together with adherence to the skin without involvement of the deeper parts. A great deal has been said of the etiology of fat necrosis. Farr produced it experimentally by traumatizing the fat tissue of pigs and also suggested that the necrosis was due to the cutting off of the blood supply. Others consider that physical trauma was absent in some of their cases, and suggest that the exciting cause is the irritation of fatty material escaped from the ducts. Certainly fatty acid crystals and cholesterol crystals are found in sections, but these may arise from the fat tissue itself. There would seem, therefore, to be two degrees of change involving fat tissue in the breast: True traumatic fat necrosis, in which there is a history of injury, physical or otherwise, and in which death of fat tissue is demonstrable microscopically, and second, a chronic inflammatory condition associated with hyperplasia of the fat cells, the result of some irritant, but not associated with necrosis. It is, of course, problematical whether the term fat necrosis should be applied to such conditions. In all the cases of fat necrosis the pathologic changes may be analyzed into those that are the direct result of injury, the actual necrosis and those in which there is the reaction to the presence of fatty acids and cholesterol, which is secondary to the necrotic changes. This reaction is shown by the endothelial and fibroblastic proliferation, foreign body giant-cell formation and the accumulation of numerous small round cells.

Infusion Treatment of Postoperative Shock.—MacFee and Boldridge (*Ann. Surg.*, 1930, **11**, 329) state that the essential fact of shock is de-oxygenation of the body tissues, whatever the absolute cause of shock may be. De-oxygenation occurs from impairment of circulation. The impairment of circulation results from diminution of blood volume in circulation. This loss is due to stagnation of blood in the capillary areas and to the escape of plasma from the capillary channels. Hemorrhage and dehydration are frequent factors. To rationally combat shock restoration of volume of blood in effective circulation is of first importance. Physiologic sodium chlorid solution has heretofore been tried as a medium to replace lost volume and has been generally discarded. By using physiologic sodium chlorid solution with or without glucose in amounts much larger than have been employed, the authors have consistently obtained gratifying results in the treatment of shock. The danger of producing acute cardiac dilatation or pulmonary edema has not been apparent in a relatively short series of cases. The authors practise and urge, however, constant vigilance during the administration of large amounts of solution. They believe that the results obtained to date with this method of treatment warrant continuation of its use.

Cancer of the Prostate.—Dossot (*J. Urol.*, 1930, **23**, 217) reports that prostatic adenoma plays an important rôle in the pathogenesis of numerous cancers; in 11.6 per cent of cases it undergoes malignant transformation. Two types of prostatic cancer should be distinguished, urethroprostatic adenoid cancer, which develops from the adenomatous glands of the prostatic urethra and true cancer of the prostate which develop from the prostate itself. The latter may coëxist with an adenoma. Cancers and adenomata are associated in 58.7 per cent of cases. Invasion of nearby organs and lymph glands always occurs in cancer of the prostate. These extensions are very early, and before they can be recognized clinically the cancer has extended widely past the limits of the glands, and has invaded the pelvic and abdominal lymph glands. Prostatectomy, radium therapy and radiotherapy have only given very mediocre results, and cases remaining cured for more than three years are the exception. True cases can only be obtained in those patients operated upon with a diagnosis of adenoma, in whom the histologic examination shows the existence of cancer. When cancer has progressed sufficiently to be recognized it has, generally speaking, extended widely. Therefore, it is prudent, at the present state of our knowledge, to limit our efforts to palliative therapy, passage of sounds and cystostomy.

Nongonorrheal Urethritis.—Costellani (*Urol. and Cutan. Rev.*, **34**, 147) claims that nongonorrheal urethrites are not of frequent occurrence, but it would appear from the author's observations that they are not so exceedingly rare or nonexistent as some authorities would seem inclined to believe. Nongonorrheal urethritis may be classified into three groups, of traumatic origin, of protozoal and metazoal origin and mycetic origin. Those of the first group are exceedingly rare, and from a practical point of view may be omitted altogether. As regards the second group, several of them are doubtful, the flagellates and some of the other protozoa found probably not being true causative agents.

The urethrites of the third group are the most important from a practical point of view as there is little doubt that the fungi found are in a certain number of cases the true causative agents. But as in the case of so many other mycoses, there is a primary and secondary mycotic urethritis. Practically all the protozoa and fungi found in nongonorrheal urethrites of the male have been found also in cases of vaginitis and vulvovaginitis, and it is not, therefore, very improbable that in certain cases and under certain circumstances these affections may be transmitted by sexual intercourse as the author suggested some years ago.

THERAPEUTICS

UNDER THE CHARGE OF

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Preliminary Report on a New Local Anesthetic—Percain.—Höfer (*Klin. Wchnschr.*, 1929, **8**, 1249), reports in detail his experiences with the use of a new substitute for cocain called percain in several hundred patients including a very wide variety of surgical conditions ranging from the most minor local operations up to extensive laparotomies for such conditions as carcinoma of the stomach, acute cholecystitis and the like. Throughout his entire experience the drug proved to be an exceptionally effective local anesthetic, its action being about twenty times as great as that of cocain. It induces anesthesia with exceptional rapidity and its action is of high intensity and exceptionally prolonged, usually the anesthesia lasting for four to twelve hours. It has the disadvantage of producing a moderate to fairly pronounced degree of local vasodilatation which, however, is readily controlled by the addition of epinephrin to its solutions. No definite toxic effects were seen in the large series of observations but animal experiments proved it to be considerably more toxic than cocain. Along with this increased toxicity and offsetting it, however, is its extraordinary degree of anesthetic potency. For subcutaneous infiltration anesthesia it is fully effective in 0.05 per cent solution which is similarly fully effective for infiltration of the deeper tissues. Its solutions in physiologic saline are easily prepared, can be boiled repeatedly without damage and can be kept for days or weeks without deterioration. For general and widespread infiltration in major operations from 50 to 150 cc. of such a solution are effective. At the time the solution is to be used 12 drops of 1 to 1000 epinephrin solution should be added for each 100 cc. The author warns against its use for splanchnic infiltration anesthesia, since in one instance this method of employment was followed by symptoms, which

might be regarded as due to intoxication. The drug itself is a synthetic, which differs entirely in its composition from other cocain substitutes, being the hydrochlorid of alphabutyloxycinchoninic acid diethylendiamid.

The Effect of Food and Other Substances on the Acid-base Equilibrium in the Human Body.—The rôle of diets in the treatment of diseases is continuously increasing. The significance of diet in therapy is due not only to its caloric content but to the chemical nature of both the organic and inorganic constituents. STRAUB (*Therap. d. Gegen.*, 1929, **70**, 481) discusses the possibilities of influencing the acid-base equilibrium in man. The acid-base equilibrium is regulated with about 1000 times more exactness than the ion equilibrium in tissues. In this regulation the kidneys, intestines and to an even greater extent the lungs play prominent rôles. A disturbance of the normal acid-base balance is especially apt to occur in diseases of these organs. In case of renal insufficiency the acidosis is due largely to intermediary metabolites. Nevertheless, the acidosis can be influenced considerably by a milk vegetable diet with its rich base content. A patient with kidney disease can be shifted with relative ease into acidosis or alkalosis depending on the food chosen. It is so characteristic of impaired kidney function that the acid-base equilibrium can easily be influenced by outside factors, especially by food, that this condition is called "poikilopikrie." In the normal individual it is exceedingly difficult to change essentially the reaction of tissue fluids. The sensitivity of the acid-base regulation varies considerably in different species of animals. The regulation is rather incomplete in the rabbit and guinea pig, it is better developed in the dog, pig and cat, and is best in man. This is an important point to remember and commands caution in transfering conclusions obtained from animals to man. Whether food can influence the composition of tissue fluids in normal man is still an open question. Undoubtedly hormones, vitamins and radiating energy have a much greater influence than food and minerals on the mineral contents of tissues. The salt content of the body cannot be influenced essentially by the administration of sodium chlorid. Phosphoric acid, calcium and other inorganic compounds, whether administered orally or intravenously, leave the blood stream rapidly and their effect is fleeting unless they enter the blood stream continuously. After the administration of unbalanced diets the alkali reserve of the blood may show considerable change. Nevertheless, as a result of the compensatory influence of respiratory regulation, the reaction of the blood changes but little. The behavior of tissue fluids is unknown. A very strict diabetic diet may temporarily produce acidosis in normal individuals, but this effect disappears within a few days. In the problem of the capacity of various ions or inorganic compounds to change the acid-base equilibrium of the blood, the chemical reaction, ionization or molecular equivalent are not necessarily determining factors. As a matter of fact, certain neutral salts such as ammonium chlorid lend themselves best to producing changes in the alkali reserve of the blood. This is due to the fact that the ammonia is changed into urea and only the hydrochloric acid equivalent of the compound remains in the body. The understanding of the influence of other neutral salts is more difficult. Meat, cereals, cheese, egg,

artichoke and legumens are acid-forming foods in the human body. Milk, the majority of vegetables, and bulbous plants such as potatoes and most fruits deliver bases in the body. It is important to remember that the method of preparation may change the behavior of food substances in the body completely. The realization of this fact is of great practical significance in dietetics. The quantitative rôle of various food substances in mineral metabolism so far is not known and therefore tables containing the acid-base equivalents of food substances can be used only with reservation.

The Action of Atophan on Hepatic Excretion of Uric Acid.—Working under conditions of accurate control KÜRTI, (*Klin. Wchnschr.*, 1929, **8**, 2239) studied the influence of atophan upon the elimination of uric acid through the bile in a group of 35 patients, among whom there were 8 with nephritis and one with orthostatic albuminuria. He administered 3 doses per day of 1 gram each of atophan by mouth to half of these and to the other half he gave ½ gram of sodium atophan intravenously just before the removal of the bile by the duodenal tube. These experiments show that in the majority of patients without renal disturbance both the oral and the intravenous administration of atophan increases the elimination of uric acid in the bile by from 30 to 50 per cent. In the group having renal disturbance the increase in elimination of uric acid is always much greater, ranging from 60 to slightly more than 125 per cent. The author concludes that the liver plays an important part in the reaction of purin metabolism and that, next to the kidneys, it is the most important organ for the elimination of uric acid. In the course of his study he also observed that the administration of atophan was followed by an increase in the daily excretion of bile, amounting to about 120 per cent.

PEDIATRICS

UNDER THE CHARGE OF

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Cisterna Magna Pressure Syndrome.—RUBEN and CHASNOFF (*Arch. Pediat.*, 1930, **47**, 201) describe a syndrome which occurs in the course of meningitis. This consists of rapid pulse, rapid respiration, a high or a low temperature and occasional delirium. They feel that it is due to pressure on the medulla and the pons by a distended cisterna. In cases due to pressure on the medulla, cisternal tap produces immediate improvement in the general condition. They advise against the introduction of serum at the first tap regardless of the character of the removed fluid. In several of their cases there was no need for further tapping. The symptoms are usually due to pressure and not to infection or toxemia. If symptoms should return, a second tap should be performed and if the fluid withdrawn is turbid and if the previous exami-

nation reveal organisms, serum should be introduced but not in larger quantities than one-half of the fluid removed. This procedure is advised even if fluid can be obtained by lumbar puncture, if the syndrome is present. In these cases the cisterna is apparently not in direct communication with the rest of the subarachnoid space so that lumbar puncture does not relieve distention of the cisterna. If this syndrome is allowed to remain without relief for as long as a week the outcome is invariably fatal.

The Blood Platelets in Newborn Infants.—JARCHO (*Arch. Pediat.*, 1930, **47**, 230) studied a series of 100 cases and found that the blood-platelet counts in normal newborn infants showed wide variations. In his series the variation was from 78,740 to 500,000 with the count in the majority of cases between 150,000 and 250,000. As a rule the platelet count is lower in newborn infants and during the first few days of life than in older children and adults. Relatively low platelet counts in newborn infants are not associated with prolonged coagulation or bleeding time except at the level of 60,000 at which point hemorrhagic symptoms may develop. There did not seem to be any definite correlation between the red-cell count and the platelet count. Not only may the total number of platelets be important but there may be qualitative changes in the platelets themselves.

Comparative Value of Viosterol and Cod-liver Oil as Prophylactic Antirachitic Agents.—DESANCTIS and CRAIG (*J. Am. Med. Assn.*, 1930, **94**, 1285) found that cod-liver oil in a dosage of three teaspoonsful daily prevented rickets in 97 of 100 cases studied. Viosterol given in a dosage of 10 drops daily prevented rickets in 77 per cent of 123 cases studied. Of the patients in this series 23 per cent developed clinical signs of rickets. Many writers have reported in large series that infants receiving no antirachitic agent at all developed signs of clinical rickets in about 25 per cent of cases. From this it would seem that viosterol given in dosages recommended by its various manufacturers is less effective in the prevention of rickets than is cod-liver oil. In the cases reported in this study the infants on viosterol received about twice as many rat units of vitamin D as those on cod-liver oil. From this it would seem that either the present recommended prophylactic dose of viosterol is too small to prevent rickets or that rickets is not due entirely to a deficiency of vitamin D. Of these two inferences, the latter seems more probable.

Asthma in Children.—PESHKIN (*Am. J. Dis. Child.*, 1930, **39**, 774) found in a series of 425 cases of asthma that the asthma remained severe, persistent and of long duration in spite of intensive modern treatment in 41 children ranging in age from two to fourteen years or approximately 10 per cent of the series. Twenty-five children, 22 of whom were sensitive and 3 of whom were nonsensitive to protein were treated by a change of environment. In spite of the fact that the inhalant and dietetic restrictions were kept less rigid than at home, 23 or 92 per cent were markedly improved or entirely relieved of asthma. Seventeen of these 25 children were returned to their homes for periods varying from six months to five years or an average of two years per patient. Thirteen

of these 17 children or 76 per cent are now greatly improved or entirely relieved from asthma. In some of these children appropriate treatment after change of environment was successful whereas it had failed before. Sixteen of the 41 children were not treated by a change of environment because of the lack of facilities and other reasons and have been used for comparison as a control. They all have continued to suffer from chronic asthma. Allergy of itself cannot be explained entirely on the basis of protein sensitization because the sensitizing substances in themselves are merely excitants and not the basic cause of the symptoms. A patient in the state of physiochemical equilibrium will enjoy freedom from symptoms in spite of exposure to exciting substances. If any factor overthrows this governing mechanism symptoms will appear. Such factors may be either specific or nonspecific or both. It is emphasized that an appreciation of this fact will aid in establishing a clearer conception of asthma and will lay the foundation of a more intelligent management of this disease in childhood. When the physiochemical imbalance has been greatly disturbed the various specific and nonspecific factors always induce asthma even though the patient is receiving appropriate treatment at the time. In these cases there is little that can be done to give relief until Nature itself restores the physiochemical equilibrium. It has been found that a change of environment preferably a home prepared to accommodate allergic patients, was of definite value in partially or completely restoring the physiochemical balance. Until newer methods of treatment are advanced with which to successfully control or free this group of children from asthma the establishment of homes where a child with chronic refractory asthma can be kept for at least six months is a very urgent humane and economic necessity as well as a therapeutic measure of definite value.

Submucous Fibrosis of the Bladder Outlet in Infancy and Childhood.—CAMPBELL (*J. Am. Med. Assn.*, 1930, **94**, 1373) states that this condition is not an uncommon condition but its recognition in the past has been extremely rare. They found that girls were less likely to have this condition than boys. Pathologically the lesion is a submucous sclerosis of the vesical orifice. The internal sphincteric mechanism may be partially but is never involved completely in the scar. Sphincteric function is interfered with giving rise to urinary obstruction associated with incomplete or difficult bladder emptying. The pathology of the urinary tract are those of infravesical obstruction and may result in renal injury. Symptomatically the lesion is evidenced by urinary frequency and difficulty, dysuria or dribbling as well as by various degrees of chronic bladder retention. Systemic symptoms when present are manifestations of uremia and are referable both to the gastrointestinal tract and the central nervous system. Infection usually is present and is the cause of a low-grade fever. The history and cystography suggest the diagnosis and cystoscopy confirms it. The treatment is surgical and consists of removal of the fibrotic mass. It is necessary to observe the same pre-operative preparation and postoperative care as for prostatectomy. Under proper conditions a satisfactory surgical outcome should be expected. The recognition and treatment of this condition early may prevent serious and fatal renal disease in later years.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Bismuth Arsphenamin Sulphonat (Bismarsen) in the Treatment of Syphilis and Other Spirochete Infections.—KOLMER (*Arch. Dermat. and Syphilol.*, 1930 **21**, 394). Bismarsen, representing a combination of two such well-known spirocheticidal agents as arsphenamin and bismuth (arsenic 12 to 15 per cent, bismuth, 23 to 25 per cent) is a distinct advance in the chemotherapy of syphilis. Kolmer reviews the work of Stokes and Chambers, O'Leary and Tobias and details his results in the experimental and clinical evaluation of Bismarsen. The feature of intramuscular administration is not only of frequent technical advantage but is of importance where slower absorption and slower elimination are necessary. Representing combination therapy as it does, it possesses the summation and synergistic effects of both drugs. Bismarsen is water soluble, rapidly diffused from the site of injection as shown by roentgenograms, and is of low toxicity in the ordinary dose of 0.2 gm. In the experimental animal, only after prolonged administration of Bismarsen in doses of 0.003 gm. per kg., occasional histologic changes were noted in the kidney. It is tolerated intravenously in the experimental animal about ten times less than that of the intramuscular route, comparable to mercurochrome and flumerin. The intravenous route is not advisable clinically, although *in vitro* Bismarsen produces neither hemolysis nor agglutination. The local reaction is usually more than bismuth in oil and usually less than of mercury salicylate or sulpharsphenamin. The use of butyn-water as a solvent has reduced the incidence of immediate discomfort but has not prevented the occurrence of a possible later local reaction. The occurrence of constitutional reactions has been low in the author's experience (800 injections), but has included hepatitis with jaundice, pruritus, tingling of fingers and toes and the "nitritoid" reaction. No hemorrhagic encephalitis or purpura with aplastic anemia has been observed, and no severe gastrointestinal reactions, gingivitis or stomatitis occurred. Albuminuria with casts was rare. Bismarsen possesses trypanocidal effects on the rat to a well-marked degree. Its spirocheticidal properties in rabbit syphilis may be expressed by a comparison of its minimum single curative dose intravenously to that of arsphenamin, that is, 0.015 gm. per kg. as compared to 0.014 gm. per kg. Intramuscularly in the rabbit it produces a slower disappearance of spirochetes and healing of the testicular lesions than arsphenamin intravenously, but

it is equal or superior to bismuth or sulpharsphenamin intramuscularly. In human syphilis the average time for disappearance of spirochetes from the initial lesion was found to be seventy hours. (Stokes and Chambers found twenty-nine hours, O'Leary seventy-five hours.) The solution of Bismarsen in butyn-water possesses marked bactericidal properties or Staphylococcus aureus and hemolytic and nonhemolytic streptococci. Clinically, Kolmer used Bismarsen in 4 cases of seronegative primary syphilis. His plan included the administration of Bismarsen every five to seven days for a course of 10 injections. After four courses and following observation of from eleven months to three and a half years there have been no serologic or clinical relapses or spinal fluid changes. Similar results occurred in 7 cases of secondary syphilis Kolmer concludes, however, that Bismarsen, because of its slower action, is less superior to arsphenamin in acute early syphilis. In latent or chronic syphilis, Bismarsen appears to its greatest advantage as (1) an intramuscular preparation of slower absorption it tends to eliminate the occurrence of a possible disastrous Jarisch-Herxheimer reaction; (2) a safer agent in testing a patient's tolerance to arsenic either after a long rest period or a previous constitutional reaction; (3) yielding good tonic effects so important in chronic syphilis, particularly tabes dorsalis; (4) representative of an ideal combination therapy for Wassermann-fast cases. It has not caused the rapid healing of late external lesions, but has afforded gradual relief from lightning pains and the headaches of syphilitic meningitis. Bismarsen was found successful in congenital syphilis, particularly for its good effect on interstitial keratitis and general tonic effects. It has not succeeded generally in completely reversing the Wassermann in these cases. Its technical advantages in young children are obvious. Finally, the author found the intramuscular use of Bismarsen valuable in 2 cases of pulmonary spirochetosis and in 6 cases of Vincent's angina.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Roentgen Treatment of Uterine Fibroids.—According to Wood (*J. Am. Med. Assn.*, 1930, **94**, 601) a large number of patients with uterine fibroids are still being operated upon who could obtain relief from their symptoms by a method which is less dangerous to life, simpler of application, and, in properly selected patients, just as effective as surgical removal with practically no mortality. His opinion is based upon 200

cases of his own which have been carefully observed. In balancing the results of the two types of treatment it is apparent that the advantages of surgery are the certainty of removal of the tumor, the possibility of avoiding sterilization in young women and the possibility of handling other pathologic conditions at the same time. Against surgery may be placed the mortality, even though low; the fact that the patient is unfit for work for at least a month, the necessary expense incident to such treatment and the disadvantages of an abdominal scar with the occasional keloid hypertrophy or ventral hernia. On the side of irradiation, radium being considered first, the advantages are that most fibroids will shrink considerably or even disappear with a single treatment of 1500 mg. hours. Menstruation may reappear after a short period of amenorrhea, in which case the patient may later become pregnant. The disadvantages of radium are that it necessitates hospitalization, the mucous membrane in contact with the radium is apt to become atrophic later or an actual constriction of the cervix with pyometra may follow, while the postirradiation sickness may be just as serious as that following surgical removal. The expense of radium is also considerable. The advantages of Roentgen treatment are that the patient is ambulant; the treatments are infrequent, being one or two weeks apart; they are short, being not over twenty minutes each; the patient as a rule does not suffer from any postirradiation symptoms; the radiation action is chiefly on the ovaries, and there is no caustic effect on the endometrium. As is well known, patients between twenty-five and forty years of age as a rule require slightly heavier dosage than those older than forty years. The reduction of a fibroid in a young woman by Roentgen irradiation without the production of permanent amenorrhea is a difficult matter and myomectomy is preferable in such instances. With modern feminine costumes, the radiation can be given without the patients having to undress which is a great saving of time for patient and operator. After the second or third dose the skin over the abdomen and back is examined to see that there is no reddening; otherwise it is entirely unnecessary to strip such patients. The patient is rarely detained more than twenty-five minutes, an important factor for those whose business or household duties make it imperative to conserve time. (A pre-irradiation curettage and histologic examination of the curettings should be invariably performed when employing either radium or Roentgen ray, in order to exclude the possibility of pregnancy or fundal carcinoma—C. C. Norris.) Neurotic patients should be told that the menstruation subsequent to the first treatments may be accentuated. It is always necessary to warn the patient about not getting sunburned or having ultraviolet ray treatment, as no matter where this sunburn is, the family physician not infrequently considers it an irradiation burn and so informs the patient. Such information greatly increases the difficulty of handling the patient and may result in threats of lawsuits or other annoyances to the radiologist, especially among the more ignorant type of patient. A study of Wood's records shows that in about 90 per cent of the private patients without complications receiving a complete series of treatments, a satisfactory clinical cure was obtained. In more than half of these there are records that there is no evidence of fibroma being present, while in the others the tumor has almost disappeared. In the dispen-

sary type of patient the results are even better because all these women desire is to be relieved of the bleeding or extreme pressure symptoms so that there are clinically fewer failures in this group than in the more highly sensitive type.

Endometrial Cysts of the Ovary.—In this country there is so much enthusiasm over Sampson's theory of endometrial ovarian cysts that it is possible that the pendulum has swung a bit too far in calling certain cysts "endometrial," when in truth they are of a different etiology. Concerning this point a mild protest has been presented by KING (*Surg., Gynec. and Obst.*, 1930, **50**, 1) of Melbourne, Australia. He states that endometrial cysts of the ovary and tarry luteal cysts possess many features in common and are indistinguishable macroscopically. Microscopically, the diagnosis requires careful study because the epithelium in both cases may be similar, the subjacent stroma in the luteal cyst may closely resemble that of endometrial glands, gland spaces may be seen in both, pseudoxanthomatous cells occur in both and the characteristic structure of the luteal cyst may not be apparent in all parts of the wall. Their similarity extends to their physiology and complications. Tarry luteal cysts sometimes rupture into the peritoneal cavity, thus producing secondary blood cysts and a severe inflammatory reaction similar to that produced by endometrial cysts. His experience suggests that the endometrial diagnosis has been made too frequently and on insufficient evidence or erroneous interpretation. The frequency with which he is able to demonstrate a luteal nature for cysts of this kind suggests that many of those recorded are possibly luteal in origin.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Gas Bubbles in the Anterior Chamber—A New Differential Diagnostic Sign of Metastatic Bacillus Coli Enophthalmitis in Diabetes.—There are in the literature a few cases in which a metastatic Bacillus coli infection has occurred in the eye. In only one of these, however, was this complicated with diabetes. None showed gas formation. REIS (*Klin. Monatsbl. f. Augenh.*, 1929, **83**, 784) reports a case in which a diabetic had a severe renal infection with Bacillus coli. Five days before death the left eye was sightless, there was pain and iridocyclitis with occlusion of the pupil. The following day there was an hypopyon. The day after Reis saw the patient for the second time; the condition of the eye then raised the suspicion of a metastatic panophthalmitis. The pupil did not dilate with atropin, the anterior chamber was very shallow. Between the iris and the cornea a few discrete gas bubbles could be plainly seen. The eyeball was not injured, nothing had been removed from the anterior chamber nor had there been any other intervention. Unfortunately it was impossible to do a bacteriological

examination after death. Three cases of gas-forming panophthalmitis are reported in the literature. In all three, however, there had been an injury to the eye. The finding of gas, which has not hitherto been observed in metastatic coli enophthalmia would indicate that the infectious agent was the same as that in the renal disease—Bacillus coli. The bacillus found favorable conditions in the eye, a nutrient medium containing sugar due to the presence of diabetes, and these conditions must have led to the development of gas, to the formation of gas bubbles. The finding of gas bubbles in the anterior chamber could thus be advanced in differential diagnosis of metastatic panophthalmus —the positive proof of gas bubbles should warrant the diagnosis of metastatic coli infection. This attempt at explanation is all the more probable since it has been shown that the vitreous is a good medium for Bacillus coli.

The Blood-sugar Content of Cataract Patients.—Because of the frequent relation between the endocrine glands and cataract, for example, diabetic cataract, the question has been raised whether senile changes in the pancreas causing an increase in the blood-sugar level may not play a rôle in the development of senile cataract, even though diabetes is not present clinically. Attempts to substantiate this by blood-sugar determinations on cataract patients have been reported in the American and the Russian literature with very contradictory results. MEHLHOSE (*Klin. Monatsbl. f. Augenh.*, 1929, **83**, 97) checked these results on 50 hospitalized patients with senile cataract, chosen with only one requirement—that the urine be sugar-free. The blood-sugar level was found to be above the upper limit of normal in only 3 patients (6 per cent). The sugar tolerance was tested in 10 patients and found to be normal. While the number of patients examined was small, Mehlhose believes that an increase in the blood-sugar level in nondiabetic patients with senile cataract is relatively rare and that the tolerance for grape sugar appears to be normal. At least an increase in blood-sugar level and a lowered sugar tolerance can scarcely be an important etiologic factor in gray senile cataract. Therefore an antidiabetic diet would scarcely halt its development.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Function of the Muscular Attachments of the Tonsil.—The effect upon the tonsil, particularly with reference to the rôle that the muscular attachments play in its function, apparently is little understood. Following a detailed description of the structural, muscular and neural anatomy of the tonsil, TROTTER (*Ann. Otol., Rhinol. and Laryngol.*, 1929, **38**, 825) presents the results of certain experiments

designed to ascertain the degree of muscular pressure exerted on the tonsil during the act of deglutition, gagging, and retching. It was observed that stimulation of the nerve endings in the mucosa of the fauces, pharynx, and tonsil causes a reflex action which affects the peritonsillar muscles. By the conjoined and simultaneous contraction of the muscles at the upper pole, the palatoglossus and palatopharyngeus muscles, and the tonsillopharyngeus muscle,[1] as well by the traction of the plica semilunaris, a series of mechanical displacements and eversion of the organ occurs, producing an expelling action or disgorgement of the tonsillar pouches and crypts. By this method the tonsillar crypts are freed of foreign material.

The Bárány Symptom Complex.—In calling attention to certain outstanding characteristics of the Bárány syndrome—such as bilaterality of involvement, absence of labyrinthine response to caloric stimulation, abnormalities of past pointing at the shoulder but not at the wrist, and pyrexia, RATNER (*Zentralbl. f. Hals-, Nasen-, u. Ohrenh.*, 1929, **14**, 263) cites the case of a twenty-one-year-old female suffering from bilateral tinnitus, auditory hyperesthesia and postauricular pain in whom there were bilateral mastoidal tenderness, altered caloric reactions, spontaneous past pointing and a continued pyrexic state. The author localizes the lesion to the cerebellopontine angle with involvement of N. V and N. VIII.

A Research on Blood Groups and Otosclerosis.—JANNUZZI (*Arch. ital. di otol.*, 1929, **40**, 499) determined the blood groupings of all the available members of five families, in each of which several persons—deaf from otosclerosis—occurred. It was ascertained that all the deaf members of a given family belonged to the same blood group. In one family all were in Group II; in another, all were in Group IV, and in the remaining three, all were in Group III. The author interprets his results as confirming the idea of an hereditary tendency in otosclerosis rather than as suggesting a possible connection with any particular blood group.

Concerning the Indications for Opening the Mastoid Process in Cases of Acute Suppurative Otitis Media, with Especial Reference to the Question of Early Operation.—From his experiences in 784 cases, HAYMANN (*München. med. Wchnschr.*, 1929, **76**, 947) has concluded: (1) That surgical intervention within the first fortnight is rarely necessary; (2) that the indications which have been promulgated by the sponsors of mastoidectomy early in the course of otitis media do not always warrant operations, and (3) that whereas early surgical interference of the mastoid process is not often a dangerous procedure, *per se*, by the same token it carries with it no guaranteed protection against subsequent complications. Inasmuch as the clinical application of his views has yielded cures in over 98 per cent of his cases, the author feels justified in pursuing his policy against premature mastoidal operations until such time as convincingly better results can be proven by adequate clinical materials.

[1] Fowler and Todd: Vide Retrospect: The Muscular Attachments of the Tonsil, AM. J. MED. SCI., 1928, **176**, 748.

RETROSPECTOR'S NOTE.—The retrospector is entirely in accord with this policy, advocating the conservative management of these cases and abstention from often unnecessary operations not only in practically all cases of acute suppurative otitis media but also in a large percentage of those presenting evidences of mastoidal involvement. While admitting the remote possibility of the exploited "sin of omission," he has yet to regret, in a single instance, having chosen not to subject a patient to mastoidectomy until the clinical, hematologic and roentgenologic findings indicated, incontrovertibly, its necessity and expediency.

Some Remarks on Deafness of Focal Infective Origin.—MACKENZIE (*Zentralbl. f. Hals-, Nasen-, u. Ohrenh.*, 1929, **14**, 262) attributes to focal infection more cases of progressive deafness than all other causes combined and eight times more instances of nerve deafness than syphilis. As frequently indicative of an infective focus is an unilateral labyrinthine involvement—often with vestibular manifestations, particularly vertigo. The inflammatory lesion may result either from the bacteria *per se* or their toxins and may be borne to the inner ear *via* blood stream or lymphatics. The importance of an exhaustive search for all possible foci of infection is emphasized—as is the necessity of their removal. It is pointed out that, in the last analysis, improvement of audition and disappearance of dizziness should follow the eradication of all demonstrable infective foci—if they are the sole etiologic factors.

RADIOLOGY

UNDER THE CHARGE OF

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Intravenous Urography by Means of Uroselectan.—In 1923 Osborne, Sutherland, Scholl, and Rowntree were the first to attempt the visualization of the urinary tract by intravenous injection of a 10 per cent solution of sodium iodid. Similar experiments were made subsequently by Rosenstein, von Lichtenberg and others. Later a synthetic compound, selectan neutral, was developed by Bing and Roth and tried by von Lichtenberg in his urologic service. This proving to be more or less toxic, Bing and Roth modified the original compound and finally obtained uroselectan, which has been employed by von Lichtenberg with a marked degree of success. Recently SWICK (*Am. J. Surg.*, 1930, **8**, 405) has tried uroselectan with equally good results. Uroselectan is nontoxic, very soluble in water, neutral in reaction, and under normal conditions excreted as such through the genitourinary tract of 80 or 90 per cent within eight hours. For an adult dose, 33 to 40 gm. is dissolved

in doubly distilled water to a volume of 100 cc. filtered and sterilized in a water bath or autoclave. Injection is made with a syringe in two stages, five minutes apart. The first examination with the Roentgen ray is made fifteen minutes after injection, a second twenty or thirty minutes later, and a third also at the latter interval. Films are also exposed at two-to four-hour intervals afterward as necessary. During injection patients experience thirst and a sense of generalized warmth. Transient nausea or vomiting may occur. It appears, however, that uroselectan is well-tolerated for intravenous pyelography and yields practical results. It has a field of application wherever ureteral catheterization is dangerous or impossible, or where mechanical or infectious factors prohibit instrumentation. In the presence of bleeding, in cases of implanted ureters, and in children, the clinical advantage of the method is obvious. Some excellent pyelograms are shown in the illustrations accompanying Swick's article. Discussing Swick's paper, Beer considered it evident that with uroselectan in the future the general practitioner with the aid of the radiologist will be able to make periodic health controls of his patients which will be accurate without relying on urinalyses and palpation. In this way, lesions of a surgical character in kidneys, ureter and bladders will be spotted at a much earlier period than at present when many patients and physicians still dread cystoscopic pyelography. Excellent shadows are obtained in hydronephrosis, in ureteral stone, kidney stone and other mildly obstructive conditions with fair renal function. Hyman also discussed Swick's paper and stated that the kidney shadow is more intense than in the ordinary pyelogram, although in general the pelvis and ureter are not as distinctly outlined as they are with retrograde pelography. With obstruction of the ureter or pelvis the intravenous pyelogram is more intense than in nonobstructive conditions.

Intranasal Ultraviolet Irradiation in Nasal Accessory Sinus Diseases.—REAVES (*Arch. Phys. Therap., Roentgen Ray and Rad.*, 1929, **10**, 488) has found that ultraviolet rays applied intranasally will abort common colds if used during the first twelve or twenty-four hours after the onset, and that they are of value in acute sinus infection and mild cases of ethmoid sinusitis in particular. In the more advanced types of chronic sinusitis it is his custom to operate and follow up with irradiation after three or four days. In atrophic rhinitis the intranasal application of ultraviolet rays helps to clear up the scabs and odor by improving the condition of the mucosa. Applications require from one to one and a half minutes, gradually increasing to three minutes, and are made daily if necessary.

Electrocoagulation of Tonsils.—Although not condemning tonsillectomy, DOANE (*Arch. Phys. Therap., Roentgen Ray and Rad.*, 1929, **10**, 495) prefers electrocoagulation on account of its comparative safety and because many patients who need tonsillectomy will not submit to a cutting operation. Electrocoagulation methods, he considers, avert danger from hemorrhage or mutilation. Age is no contraindication Special instruction in the procedure is necessary. Among the various methods, the author has a preference for the bipolar high-frequency current.

Roentgenologic Studies of the Mastoid in Infants.—After the age of six months a cavity having the shape of the mastoid can be demonstrated below the tegmen tympani and behind the external auditory meatus in good roentgenograms, according to MARTIN (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 431). This cavity varies markedly in size and may measure $\frac{3}{4}$ inch in diameter and show definite cell structure by nine months, although such excessive development is unusual. Diploetic mastoids are probably diploetic from the start, whereas cellular mastoids begin as large single cavities, which slowly increase in size and usually begin to show cellular structure at nine to sixteen months. The presence of pathologic conditions of the mastoid can usually be detected in good roentgenograms after the age of six months, though double infections often make interpretation difficult.

Zinc Ionization in the Treatment of Intumescent Rhinitis.—The broad indication for intranasal ionization is intumescent or early hypertrophic rhinitis, according to GALE (*Arch. Phys. Therap., Roent. Ray and Rad.*, 1929, **10**, 486) and his results have been favorable. The method consists of packing the side of the nose to be treated with long, narrow strips of gauze saturated in a weak zinc solution. This solution is made of 1 per cent, or less, of zinc sulphate and distilled water to which a very small amount of glycerin has been added. After the packing, a zinc or copper wire is inserted into it and connected with the positive terminal of a galvanic apparatus or battery cells. The indifferent electrode, which is made of a moist pad, is applied to the forearm or other body surface, and connected to the negative terminal. The current is now turned on. From 3 to 10 ma. of current are tolerated comfortably by the average patient. The treatment consumes about fifteen to twenty minutes. The patient will complain of a metallic taste and temporary salivation, but no other disagreeable symptoms. After the packing is removed, a white coating may be observed on the turbinates and septal membranes. After twenty-four hours the membranes present a grayish appearance and a day or so later a definite shrinkage is observed. The turbinates lose their bogginess and approach a normal tendency. All untoward symptoms disappear in three days. Improved ventilation and drainage are the direct result. Only occasionally is it necessary to repeat the treatment. If a second treatment is necessary it should not be given in less than ten days to two weeks.

Nontraumatic Diaphragmatic Hernia.—Seven cases of diaphragmatic hernia are reported briefly by ELWARD and OTELL (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 535). In every case save one a portion of the stomach had herniated through the esophageal hiatus, and the condition was demonstrable with the Roentgen ray. The hiatus is practically a slit in the muscular portion of the diaphragm, which happens to be the most easily distensible portion of the structure. The history of these cases not infrequently shows a more or less protracted period of transient increases of intraäbdominal pressure, such as would result from the violent coughing in pertussis or chronic bronchitis, straining at stool,

or the second stage of labor, and one can understand why herniation in this area should occur. Clinically, the picture presents a right upper quadrant syndrome, simulating cholecystitis, or gastric or duodenal ulcer. The most constant symptoms are pain in the epigastrium, regurgitation and abdominal distress on assuming a recumbent position. The diagnosis can be made with certainty only by means of the Roentgen ray, carefully studying the lower esophagus with the patient in various positions. Distinction must be made from cardioesophageal relaxation, diverticulum of the lower end of the esophagus, diverticulum of the stomach, cardiospasm, hour-glass stomach, cancer, perforation of the esophagus and congenitally short esophagus.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Cerebral Circulation.—WOLFF (*Arch. Neurol. and Psychiat.*, 1929, **22**, 686) reports on the action of acetylcholine, the extract of the posterior lobe of the pituitary gland, and amyl nitrite on the cerebral circulation, in three separate articles. The method consists of observation by means of a microscope, through a window in a trephine opening in the skull. With acetylcholine injected intravenously he found dilatation of cerebral arteries, veins and minute vessels with usually a rise in cerebrospinal fluid pressure and a fall in systemic arterial pressure, and is able to show that the chemical content of the blood has more effect in regulating the diameter of cerebral bloodvessels than its hydrostatic pressure. Extract of the posterior lobe of the pituitary gland caused constriction of pial arteries, arterioles and minute vessels, again showing the effect of the chemical content of the blood. With amyl nitrite he found a dilatation of cerebral vessels with a fall in systolic arterial pressure and rise in cerebrospinal fluid pressure. The experiments were conducted on cats.

Malaria as a Therapeutic Agent for Paresis.—DE ASIS (*Arch. Neurol. and Psychiat.*, 1929, **22**, 752) reports on 101 cases treated in the Worcester State Hospital with benign tertian malaria. He finds no apparent relationship between the clinical results of treatment and the number of paroxysms and his only criterion for deciding how many chills a patient may have is his general condition, except that not more than 18 paroxysms are allowed in a given case. He terminates the malaria by quinine administered by mouth and cautions against its intravenous use. Complications during the treatment were herpes labialis, jaundice

cachexia and anemia, 2 cases of ruptured spleen and one of cerebral hemorrhage and edema. Serologically he finds few changes in either the blood or spinal fluid. Clinical results were as follows: Markedly improved, 32.6 per cent; improved but unfit for visit home, 15.8 per cent; unimproved, 31.6 per cent; aggravated, 0.9 per cent; relapsed, 2.9 per cent; died directly or indirectly from malaria, 7.9 per cent; died from other causes, 7.9 per cent. He believes that the therapy should be administered in every case in which the physical condition does not contraindicate its administration.

Schizophrenia and Psychotherapy.—BRILL (*Am. J. Psychiat.*, 1929, **9**, 519) believes that only those acute schizophrenics who cannot be kept at home should be sent to sanitariums and they should only stay there until the acute process subsides. He calls attention to the hopeless prognosis formerly held in reference to schizophrenia and Professor Freud's early suggestions that cases of dementia precox should not be psychoanalyzed. He presents a group of cases which made excellent adjustment when treated without hospitalization and were successfully carried through to a conclusion of their illness with good insight and good adjustment. He believes that since the essence of the schizophrenic psychosis is a withdrawal from the world of reality that hospitalization in cases where it is not absolutely necessary tends to favor the withdrawal and to fix the individual into an institutionalized adjustment from which it is very difficult to release him. "As disagreeable as this may sound to you, it is none the less true that practically all the hospitals and sanitariums for mental diseases seem to be especially arranged to bring about this very sad result." In those cases where hospitalization is necessary the patient should be discharged from the hospital as soon as possible, but all of these patients must be followed over a very long period of time in order to prevent recurrences of the condition and to insure a continuation of the adjustment reached.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Sensitization to Saprophytic Fungi.—Comparatively little has been written on the sensitization of human beings by the spores of common saprophytic fungi. The spores of a great variety of these fungi are practically universally distributed in the air. A patient with asthma and eczema, studied by HOPKINS, KESTEN and BENHAM (*Proc. Soc.*

Exper. Biol. and Med., 1930, **27**, 342) was found to be sensitive to a species of Altenaria by skin and inhalation tests, as well as to a common saprophyte Aspergillus nidulans isolated from an eczematous lesion of the leg, and to other fungi obtained from house dust. The authors had some difficulty in interpreting certain of their results because of the known sensibility of eczematous skin to nonspecific irritation.

Intestinal Bacterial Flora and Microbic Permeability in Relation to Nutritional and Meteorologic Changes.—Disturbances in the equilibrium between parasites and the host must be more fully recognized if we are to understand the importance of the varying factors in certain diseases. ARNOLD (*J. Hygiene*, 1929, **29**, 82) has studied among such factors, the influence of sudden changes in the acid-base equilibrium in inhibiting the destruction of bacteria by the intestinal mucosa, and in permitting the penetration of bacteria into the thoracic duct. Climatic changes have been shown to affect the susceptibility to infection, and nutritional factors must be considered as inseparable from those of climate. The beneficial effect of a changing nutritional and meteorologic environment on the tonus of the physiologic systems is emphasized, but it is also indicated that these alternations in environment must not exceed the power of the organism to adapt itself to these changes. The bearing of these principles on the incidence of seasonal outbreaks of various intestinal diseases is discussed and much experimental evidence is presented in demonstration of his thesis.

Immunization of Chickens Against Fowlpox.—A variety of methods have been used in the preparation of materials for vaccination against fowlpox. KLIGLER (*Brit. J. Exper. Path.*, 1930, **11**, 10) treated the infectious materials obtained from the skin lesions by heat, formalin and phenol. The crusts from the skin contain active virus in large quantities, and lend themselves for the production of a vaccine. The author found that fowlpox virus heated to 56° C. for one hour, or treated with 0.5 per cent formalin solution for four days no longer infects susceptible chickens, and fails to produce immunity. Phenolized vaccine (0.25 per cent) contains active virus from three to seven weeks after preparation and though this will no longer induce active lesions, it will produce immunity. The failure of heated phenolized vaccine to produce immunity while the same material unheated will protect, indicates that the immunity was induced by a living virus.

Mixed Tumors of the Palate.—The term mixed tumor is applied to histologic complex neoplasm in which a variety of tissue elements constitute a part of the progressive growth. These tumors arise, not uncommonly, about the face and mouth, being most frequently observed in the parotid gland. D'AUNOY (*Am. J. Path.*, 1930, **6**, 137) reports two cases of mixed tumor of the palate in women aged twenty-five and forty-three years respectively. The tumors were similar in type both being encapsulated masses, made up of glandular tissue embedded in a myxomatous cartilaginous stroma. Attempts at epithelial keratinization were observed in one of them. These tumors, in this location, are not common, there being less than one hundred in the literature. For

the most part, mixed tumors possess only a local malignancy, and will recur if not completely removed. There is no agreement, up to the present time, as to the origin of the individual elements composing the mixed tumor. The author leans to the theory of embryonal enclavement.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Postvaccinal Encephalitis.—ARMSTRONG (*Pub. Health Rep.*, 1929, **44**, 2041) notes that nervous manifestations have long been known to follow such acute infections as smallpox, chickenpox, measles, mumps, etc. Postvaccinal encephalitis belongs to this group. The history of the complication is reviewed, several hundred cases having occurred in Europe. The onset is usually sudden and occurs from the tenth to the thirteenth day after vaccination—that is, when the vaccination is at its height. The symptoms are fever (104° F. or more) vomiting, headache and stupor or coma. Death occurs in from 30 to 40 per cent of cases. Recovery, when it occurs, is rapid and complete, save in a few cases where crippling results. The cause of the complication is unknown; animal tests have been negative. Several cases have occurred in the United States and it is suggested that reports of cases observed be made to the U. S. Public Health Service.

Leprosy.—During a clinical study of leper patients in Hawaii, WAYSON and BADGER (*Pub. Health Rep.*, 1929, **44**, 2871) obtained findings suggestive of disturbances of carbohydrate metabolism with remarkable frequency. About 23.4 per cent of the cases showed glycosuria and the percentage of positives was markedly increased by feeding glucose. It was also found that the average basal blood-sugar percentage was higher than normal. The excess of sugar in the urine was larger among female patients. The tests were controlled by the examination of blood and urine of nonlepers. The writers regard these findings as indicative of a high incidence of carbohydrate metabolism among lepers. They point out that leprosy affects chiefly the skin and nerve tissues and that in diabetes these tissues are also often involved. WAYSON (*Ibid.*, 3095) has analyzed the results of the treatment of lepers in Hawaii over a period of many years. Medical treatment, chiefly with respect to chaulmoogra oil and its derivatives, is described and reference is made to symptomatic and hygienic measures.

With respect to the latter, an attempt is made to place all patients under hygienic and sanitary conditions which will contribute to their general health and favor the marshaling of their resistive and reparative forces. Definite conclusions concerning the efficacy of these methods in hastening or accomplishing recovery from leprosy cannot be drawn at this time, but their apparent efficacy in the treatment of analogous diseases, and the results thus far obtained in leprosy seem sufficient to warrant their expansion and more intensive application while investigations are continued toward the development of more definitely remedial measures or agents. The number of annual admissions and the probable rate of incidence of leprosy in Hawaii are both falling, and it appears that biologic and other agencies may be causative factors in the decline, and that the effect of the mandatory segregation of cases for the past sixty years is indefinite. However, the measure seems to be economically feasible, and is justifiable and desirable in the community, because of its potential value in controlling the dissemination of the disease, and because of its value in facilitating the treatment of the individual patient and the investigation of the pathogenesis and treatment of the disease in general. The use of chaulmoogra oil and its derivatives in Hawaii for ten years has not been attended by results which indicate that they have any specific therapeutic value, and any effect they may have remains undetermined. Symptomatic and hygienic treatments under hospital or sanitarium régime probably aid in the recovery of some patients; but further properly controlled observations over several years are needed to determine this. Studies of pathogenesis, early diagnosis, and treatment with the facilities offered to modern medical research are required for the promotion of more effective results than are being obtained. DENNEY (*Ibid.*, 3169), who studied leprosy in the National Leper Home at Carville, La., remarks on the hopeful outlook in the treatment of the disease in a considerable number of patients. During the fiscal year 1928–1929, among a leper population of about 300, 19 were released as arrested cases and no longer a menace to the public health. Six additional cases might have been placed in the same class but were retained in the hospital for humanitarian reasons. About half the patients take chaulmoogra oil by mouth and about the same number take it by hypodermic injection. A few take the ethyl ester preparations. The various services furnished by the hospital are described briefly. About a third of the patients give a positive serologic test for syphilis. Tests were made on the sputum of 210 lepers and of these 99 showed acid-fast organisms. Seventy-five of these were tested by guinea-pig inoculation and 14 were positive for tuberculosis.

Vaccinia: Studies of Immunity, Reactions and Effects of Heat.—ANDERVONT and ROSENAU (*J. Immunol.*, 1930, **18**, 51) obtained a reaction following the introduction of heated vaccine virus into the skin of previously vaccinated persons. This was noted during the course of experiments in which heated material served as "control" for unheated virus. These experiments confirm the findings of others and also indicate that with the single scratch method of vaccination, virus heated to 70° C. for one hour, kept in boiling water for one hour, autoclaved for one hour or kept at room temperature for five years is capable of eliciting the response in previously vaccinated individuals; in fact, the

reaction following the use of heated virus was as constant as that observed when unheated virus was employed. The reaction to heated virus appears and disappears somewhat earlier than the reaction to unheated virus. The heated virus produces a reaction with papules indistinguishable from the well-known immediate reaction. It was also found that no reaction occurs when heated virus is used to vaccinate previously unvaccinated children or adults, and that such vaccination induces no immunity. The writers' studies concerning the antigenic substance responsible for the immediate reaction tend to show that the virus is the causative factor. An extract of vaccine pulp freed of virus by filtration is incapable of causing the reaction. Furthermore, individuals immunized against cowpox by vaccination with calf virus give the immediate reaction when revaccinated with vaccine virus derived from rabbit brain. These results indicate a common antigen in calf and rabbit material. The vaccine virus is known to be present in both. The possibility of another antigenic substance being responsible is excluded because normal calf skin or glycerinated normal rabbit brain fail to evoke any reaction in previously vaccinated persons.

The Epidemiology of Diphtheria and Scarlet Fever in the Subtropics with Special Reference to the Syrian States Under French Mandate.—PARR, GOODALE and KIRSCHNER (*J. Prev. Med.*, 1930, **4**, 39) performed Dick tests on 714 and Schick tests on 878 persons living in the Syrian States under French mandate and found that the people of this area possess a remarkably high resistance to the toxins of diphtheria and scarlet fever. A study of government reports of morbidity and mortality and a medical census of 2301 persons show that clinical cases of scarlet fever are very rare and that diphtheria is only slightly more common. It is suggested that subclinical diphtheria is common and that it is probably the cause of the diphtheria immunity. As regards scarlet fever there is less evidence that subclinical immunization is responsible for the existing immunity. In view of prevalent streptococcal infections of the throat and middle ear and the low puerperal sepsis rate, it is possible that immunity against puerperal sepsis and scarlet fever is built up at an early age by infections with the streptococcus in other and milder clinical forms. Measles is common in the area in question. This lends support to the view that the etiologic agent of this disease has no very close relationship to that of scarlet fever. Further, for tropical and subtropical countries at least, measles may be thought of as a younger disease than either diphtheria or scarlet fever.

Current Studies of Undulant Fever.—HASSELTINE (*Pub. Health Rep.*, 1929, **44**, 1659) discusses the present status of undulant fever in the United States. The disease was reported in this country first twenty-four years ago when Craig reported a case and prophesied that it would be found to account for some of the " . . . obscure continued fevers which are prevalent. . . ." The disease is now being recognized quite frequently. The prevalence seems to vary greatly in different parts of the country. The diseases likely to be confused with undulant fever are tuberculosis, typhoid and paratyphoid fevers, rheumatism, malaria, influenza, focal infections, tularemia, and a few others. The chief symptoms are weakness, headache, or general aching, fever, chilli-

ness or chill and profuse sweating. The sweating is often confined to the upper half of the body. The temperature may be normal in the morning and go to 104° F. in the afternoon. Characteristic febrile waves may occur separated by afebrile periods. Some cases have only one wave; others have recurrences during one to three years. Diagnosis is aided by positive agglutination titer in the serum and made positive by a successful blood culture. The infection seems to originate most often with cows, less frequently swine and rarely goats. Persons may acquire the disease from handling infected animals, or animal products, or by the use of milk from such animals. The ideal prevention would be the elimination of the disease from animals, and this is believed to be a possibility. Pasteurization, or boiling, of milk would prevent milk-borne cases.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 19, 1930

Hair Groupings in the Skin of the Albino Rat.—D. A. FRASER (from the Department of Anatomy, University of Pennsylvania). The arrangement of hairs into groups was studied on the dorsum and on the venter in microscopic sections cut at right angles to the length of the hair follicles. Groups may be considered in two classes, for example, those with and those without a central follicle, which must contain a hair twice the diameter of the other hairs in the group. Follicles can be classified according to their location within a group, as central, containing a central hair; adjacent, the remaining follicles within such a group; and associate, those in groups without a central follicle. Follicles may be single, or composite, that is, containing more than one hair. The hairs in groups with a central follicle average 13.9 on the dorsum and 17.2 on the venter, distributed in 6.05 and 7.4 follicles, respectively. Hairs in groups without a central follicle average 8.7 on the dorsum and 9.7 on the venter, distributed in 3.8 follicles in both cases. During the winter months there are 7.7 groups, 35.75 follicles and 85.65 hairs to an average square millimeter of dorsal skin and 11.5 groups, 54.7 follicles and 152.60 hairs to an average square millimeter on ventral skin. It is estimated that the body hairs number 5,028,303 in the male albino rat of 230 gm. of body weight. It is hoped that these counts can be used as a standard for those experimentalists who report the hair as being more luxurious or more sparse as a result of dietary or endocrine conditions.

Comparison of the Hydrogen and the Glass Electrode in the Determination of the pH of Serum.—W. C. STADIE and H. O'BRIEN (from the Department of Research Medicine, University of Pennsylvania). A simple glass electrode was constructed which can be maintained at 38° C. and by which the pH of serum or whole blood may be deter-

mined with a high degree of accuracy. One to 2 cc. of serum is required which is collected by a technique which prevents loss of carbon dioxid and transferred to the electrode from a syringe or mercury receivers. Equilibrium is reached in two to four minutes, and E.M.F. of the glass cell is read to within ±0.1 mV. by means of a stable and sensitive electron tube potentiometer. Various controls were done to show the reliability of the method. A series of sera were compared as to their pH by the hydrogen electrode and the glass electrode and a close agreement found which averaged about ±0.007 pH units.

The Structural Composition of the "Bone Solid."—S. E. POND (from the Laboratory of Physiology, University of Pennsylvania). Two series of experiments are reported which are part of a study of the inorganic composition of bone and homologous tissues. They were planned to add to information concerning the bone phosphate. Previously it had been shown that the ratio:

$$\frac{\text{Total inorganic } P_2O_5}{\text{Total CaO, less CaO evivalent to } CO_2}$$

had yielded values indicating the calcium phosphate in bone to be more basic than tricalcium phosphate. It was not known whether the ratio as calculated was a true index of the phosphate component and particularly the calcium phosphate, since the combination of calcium with protein and with carbonate had not been measured.

The material studied was bone which had been prepared from whole skeletons of rats and rabbits grouped as to age. The marrow lipoids were removed by hot alcohol. Drying was done over sulphuric acid. Analyses of the bone powder were made by several methods found to yield satisfactory results in the study of the inorganic materials concerned. The data represent ash, total CO_2, CaO, P_2O_5 and MgO, with respect to age. This dried powder was used to determine: (*a*) the calcium bound by protein and (*b*) differences in solubility of material as a guide to the molecular structure of calcium phosphate in bone.

A. Samples of powdered bone were treated with 0.5 N HCl in small portions and leached with 0.001 N HCl until calcium-free. This powder was adjusted to pH 3 in dilute acid and found to retain no calcium from calcium chlorid solution. Samples of the same powder were ashed and found free of calcium. Portions were adjusted to pH 5.5 and found to retain calcium. The amount of calcium bound by the powder at pH 5.5 was measured by removing in acid solutions and analyzing as oxalate. The amount was different for bone from adult and from newborn skeletons, viz.: 0.95 mM Ca per gram dry isoelectric powder and 0.7 mM Ca per gram dry powder, respectively. Deaminized powder from adult skeletons was found to combine with 0.92 mM Ca per gram dry isoelectric powder. The results indicate a combination with some ampholyte and apparently with carboxyl groups. The amounts are significant, and indicate some differences in combining power with respect to age. The experiments are being continued with standardized laboratory animals of known age representing four species.

B. Several attempts to secure calcium-free powdered bone for the above study had demonstrated a marked difference between the

inorganic components of the bone from adults and from very young animals when used in acid solutions. Powdered bone from whole skeletons of newborn animals (rat and rabbit) was made calcium-free in dilute acid solutions and in salt solutions between pH 3 and pH 4. Bone from adults required stronger acid solutions, such as 0.5 N HCl, to dissolve the calcium phosphate. Powdered bone from adults when treated and leached on filters could only with difficulty and with excessive amounts of reagent be freed of calcium when 0.05 N acid solutions were employed as solvents. The same material when so treated or shaken for long periods, but with 0.005 N HCl and with HCl:Na acetate adjusted to pH 2.03, retained over 80 per cent of the total calcium.

A graded series of solutions with respect to pH was employed to indicate differences in the calcium phosphate. This consisted of HCl = 0.5 N, 0.1 N, HCl:KCl pH 0.94 and pH 1.87 and HCl:Na acetate 1.09, 2.03, 4.19 and 6.31.

1. Bone from newborn animals: all of Ca, Mg, P and CO_3 dissolved in pH 4.19. Shaken sixteen hours at 25° C.; solutions changed after two, four and eight hours.

2. Bone from adults: all of Mg and CO_3 dissolved in pH 4.19, but only 15 per cent of total P and 20 per cent total Ca. Shaken sixty-four hours, as above, except solution changed after sixteen hours.

Complete solution in pH 1 HCl, in pH 0.94 HCl:KCl and pH 1.09 HCl:Na acetate but not in pH 1.87 HCl:KCl nor HCl:Na acetate pH 2.03 within limits of experiment.

It is concluded that the bone phosphate has a different composition with advancing age and is no more basic than $Ca_3(PO_4)_2$ in the bone of embryos and newborn animals examined. Some more basic phosphate is present in bone of older animals. The structure of this material is being studied further with chemical and physical criteria.

Experimental Study of the Van den Bergh Reaction.—J. G. REINHOLD and H. F. SNIDER (from the Biochemical Laboratory of the Philadelphia General Hospital). A close relationship exists between the concentration of bilirubin in serum, estimated as icterus index, and the type of direct van den Bergh reaction. Immediate reactions were associated with high bilirubin values and delayed reactions with low values. Between these extremes biphasic reactions were most frequently observed. Working on the hypothesis that speed of color formation after the addition of diazo reagent might be governed by variations in the concentration of bilirubin in the serums, the behavior of solutions of pure bilirubin in human serum was studied. A series of such solutions containing approximately the quantity of bilirubin found in the serum in jaundice showed progressively negative, delayed, biphasic and immediate reactions as the concentration increased. Pathologic serum of the immediate reaction type diluted with normal human serum also was converted to the biphasic, delayed, or negative reaction type, depending on the degree of dilution. Delayed reactions became biphasic when the temperature of the reacting materials was increased from 15° to 30° C. Other factors, such as hydrogen-ion concentration, capable of changing the type of reaction, ordinarily do not vary enough to influence appreciably the interpretation of the test.

Therefore, the results given by the direct van den Bergh reaction depend upon the concentration of bilirubin in the serum and not upon changes in the molecular or physical state of the bilirubin.

The Action Potential Wave in Nerve During and After Oxygen Lack.—W. R. AMBERSON, A. PARPART and G. SANDERS (from the Laboratory of Physiology, University of Pennsylvania). The low-voltage components of the single action potential wave[1] have been followed in frog nerve, during and after a period of oxygen lack. The "after positivity" quickly disappears in pure nitrogen. The negative retention is at first exaggerated and then suppressed, long before the disappearance of the high-voltage phase of the wave. Upon the readmission of air the negative retention reappears again within a few minutes and becomes very highly developed, producing a rise in maximal deflection of the galvanometer to values much exceeding those previously obtained in air or in nitrogen. An "after positivity" also reappears.

By a direct method of analysis it has been found possible to follow the time relations of both high- and low-voltage phases of the action potential wave. The initial high-voltage phase undergoes no such changes as are seen in the low-voltage elements which succeed it. In nitrogen the high-voltage phase continues for several hours unchanged, then slowly is reduced to nothing; upon the readmission of air it quickly recovers its original value. No postasphyxial overshoot is seen. It is concluded that the two elements of the action potential wave are the electrical signs of two separate processes, one of which, associated with the high-voltage phase, is relatively anaërobic, while the other, presumably a recovery mechanism, connected with the persistent low-voltage elements, is relatively aërobic in nature. At least it may be stated that the retentions are much more sensitively related to the presence or absence of oxygen than is the high-voltage phase.

[1] Amberson and Downing: J. Physiol., 1929, **68**, 19.

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SPECIAL MINUTE CONCERNING THE DEATH OF DR. PAUL A. LEWIS

AUTHORIZED AT THE SESSION OF OCTOBER 21, 1929

In November, 1928, Dr. Paul A. Lewis offered his services to the Rockefeller Foundation for the accomplishment of a project to extend the study of yellow fever in South America, earlier made by his friend Noguchi. His offer was accepted; and from January 15 to June 25, 1929, he worked in the laboratories of the International Health Commission in Bahia, Brazil, on the nature of the virus of yellow fever. On the latter date, he was stricken with that disease and died on June 30, 1929.

Paul Adin Lewis was born in Chicago, Illinois, on April 14, 1879. His father was a physician, and as a boy he used to drive the horse on his father's professional visits. From this association a passion grew in him to become a "good doctor." His medical training was obtained in the University of Pennsylvania, where he graduated in 1904. Here, under the inspiration of Flexner, he developed an interest in research in pathology and he soon came to feel that his ambition to be of service to medicine could best be accomplished in a career of investigation. After graduation he served as interne in pathology in the Boston City Hospital under Dr. Frank B. Mallory. The following three years, 1905–1908, he came under the influence of Professor Theobald Smith in the Massachusetts State Laboratory of Health and for two of these years held the Austin teaching fellowship in pathology in the Harvard Medical School.

The years 1908–1910 were spent in work at the Rockefeller Institute in New York in direct association with Simon Flexner. In 1910 he came to Philadelphia as director of laboratories of the Henry Phipps Institute of the University of Pennsylvania, a position he held until 1923. During all of this time he was also a member of the Medical Faculty of the University, first with the title of Assistant Professor of Pathology (1910–1921), later as Professor of Experimental Pathology (1921–1923). He also served as director of the Ayer Clinical Laboratory of the Pennsylvania Hospital from 1911 to 1916. In 1923 he resigned from his positions in Philadelphia to become associate member of the Rockefeller Institute, electing to serve with Theobald Smith in the Institute of Animal Pathology at Princeton. From Princeton he went to Brazil.

Thus for almost exactly twenty-five years he devoted his best energies to investigations in pathology. The results of his work were conspicuous and secured for him both a national and international reputation as one of our most competent pathologists. He and Auer were the first to discover the mechanism of anaphylactic death in guinea-pigs. His work with Flexner on poliomyelitis and on the nature of poliomyelitis virus is classical and his part in this was more than that of subordinate assistant.

During the first years of his directorship of the Phipps Institute he organized a staff for the comprehensive study of the chemotherapy of tuberculosis, believing with firm conviction that a specific agent against this disease is to be found. His hope was not realized, but the results of his study of hundreds of compounds may serve as a sound foundation for future work in this field.

In collaboration with Sewall Wright of Washington, using guinea-pigs whose heredity was known for many generations, he made masterly beginnings of a descriptive and analytical study of heredity factors in susceptibility and resistance to tuberculosis, discovering the fact that the inheritance of resistance is a dominant trait in the Mendelian sense. He discovered and described as "allergic irritability" the heightened capacity of the animal body, infected with tubercle bacilli, to react to nonspecific substances with increased production of antibodies.

His early developed interest in filterable virus was continued in his Princeton period in studies on hog cholera and on hog influenza, the latter giving promise in his opinion of important developments in relation to pneumonia in man. This interest was an important factor in his decision to volunteer to study the yellow-fever problem.

We are as yet ignorant of the permanent value of his studies of yellow fever. He himself did not rate them very highly. He went to South America knowing that it would be extremely difficult to add materially to the work of Noguchi, but he was impelled to undertake the task chiefly because of loyalty to a close friendship of twenty years.

During the World War, Dr. Lewis searched for ways of making his capabilities valuable to the medical services of our forces. Very soon after our entrance into the war he organized a group of four workers, of which he was one, to aid the Surgeon-General of the Army in discriminating among the various means, urged upon him, for combating infections. Later in the summer of 1917 he volunteered for service in the Navy, was commissioned Assistant Surgeon with the rank of Lieutenant (Junior grade), and with the permission of the University authorities placed the laboratory of the Phipps Institute at the disposal of the government. The laboratory became the central station in this district for the production of typhoid vaccine, and from it he directed bacteriologic surveys for the detection of meningococcus carriers among the Navy personnel. His services were recognized by successive promotions to the grade of Medical Inspector with the rank of Commander.

The most conspicuous qualities of his character were courage, loyalty and unselfishness. The force which these qualities gave to his investigative insight and zeal made him one of the most influential factors in the development of medical science in Philadelphia during his years here. His courage was exhibited in the difficulty and magnitude of the problems which he chose for study; in the plans which he made and fought for in the institutions with which he was connected; in his decision to abandon his influential directorship of the laboratories of the Phipps Institute in order that his own scientific efforts should not be impeded by administrative duties; and finally by his decision to volunteer in the yellow-fever work.

His loyalty to his profession, to the community, and to the University was demonstrated repeatedly in the plans which he constantly advocated for greater utilization and extension of the methods of research in their medical problems. He was a leader in almost every one of the organizations in Philadelphia devoted to medical research,

among them the Physiological Society of Philadelphia. Evidence of his unselfishness is to be found not only in the record of his deeds but in the affection in which he was held by those who were associated with him in his work. Not only was he a wise counsellor but in numberless instances he was the author of plans by which the work of his colleagues could be made happier or more productive.

The preparation of this statement is dictated by the desire of the members of this Society that its permanent records shall contain an expression of their sense of loss because of the death of a loved colleague, and by the hope that they may reveal the basis for feelings of pride cherished by the members in his spirit, his accomplishments and the circumstances of his death.

The Roll of Honor of this Society now holds two names:

ALFRED REGINALD ALLEN

who was killed on the field of battle in France in 1918

and

PAUL ADIN LEWIS

who died as a volunteer in the fight against yellow fever.